CHEST Clinical Commentary

α_1-Antitrypsin Augmentation Therapy for PI*MZ Heterozygotes*

A Cautionary Note

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The use of IV augmentation therapy with plasma-derived α_1-antitrypsin (AAT) has become the standard of care for the treatment of pulmonary disease associated with the severe genetic deficiency of AAT. The Medical and Scientific Advisory Committee of the Alpha-1 Foundation has become aware that physicians are prescribing this expensive blood product for the treatment of individuals with a single abnormal AAT gene, primarily the PI*MZ genotype. We are aware of no evidence that such therapy is effective in this patient population. The most important therapeutic interventions in such patients remain smoking cessation and elimination of other risk factors for lung disease. This commentary discusses the treatment of AAT deficiency and the concerns regarding treatment of PI*MZ individuals. We conclude that clinicians should avoid prescribing augmentation therapy for this heterozygote population. ***(CHEST 2008; 134:831–834)***

Key words: α_1-antitrypsin deficiency; genetics; heterozygote

Abbreviations: AAT = α_1-antitrypsin; MASAC = Medical and Scientific Advisory Committee of the Alpha-1 Foundation

Severe deficiency of α_1-antitrypsin (AAT) [defined as having a serum level below the "protective threshold" value of 11 μmol or approximately 50 mg/dL using nephelometry] is a common but underrecognized condition that can predispose to COPD and to chronic liver disease.[1–3] Augmentation therapy with purified pooled human plasma AAT represents the only specific available therapy for lung-affected individuals with severe deficiency of AAT. In the face of concordant observational studies but no definitive supportive randomized controlled clinical trials to date, augmentation therapy has been endorsed by official societies[1] for severely deficient (*eg*, PI*ZZ), symptomatic individuals with a component of irreversible airflow obstruction and/or emphysema. Notably, in the complete absence of any data suggesting efficacy for individuals with PI*MZ AAT deficiency, available guidelines do not endorse use of augmentation therapy for such individuals. Three drugs for augmentation therapy—Prolastin (Talecris Biotherapeutics; Research Triangle Park, NC), Aralast (Baxter Healthcare; Deerfield, IL), and Zemaira (CSL Behring; King of Prussia, PA)—are currently available in the United States, all of which are costly (estimated $60,000 to $150,000 per year[4]).

The original dose-finding study[5] leading to the current dosing recommendation for all the currently available commercial products was aimed at achieving blood and epithelial lining fluid levels of AAT protein in severely deficient individuals that approximate those seen in PI*MZ individuals not on augmentation therapy. In the context that augmentation therapy is expensive (to the recipient of such therapy, his/her insurer, and the health-care system in general), can be associated with side effects (however uncommon[6]), and has been subject to intermittent supply interruptions, there is an obvious imperative to optimize utilization of augmentation therapy. Optimal use includes ensuring the prescription for and use of augmentation therapy by candidates

deemed appropriate for its receipt based on current understanding of its efficacy and role. Yet, as with "off-label" use of many drugs for sparsely studied or validated indications,[7] we, the members of the Medical and Scientific Advisory Committee (MASAC) of the Alpha-1 Foundation, have become aware that augmentation therapy is currently being made available to and used by individuals who are heterozygous for AAT deficiency (*eg*, PI*MZ individuals). PI*MZ individuals may comprise approximately 10 million Americans (3.6% of the US population).[8] In screening all individuals with COPD or incompletely reversible asthma as suggested by guidelines,[1] the likelihood of a physician encountering an individual with PI*MZ is substantially higher than encountering an individual with PI*ZZ.

As members of the MASAC,[9] our purpose in this commentary is to offer a cautionary note regarding prescribing augmentation therapy for individuals other than those endorsed for its receipt based on the best current evidence (*eg*, symptomatic, lung-affected severely deficient individuals with a component of irreversible airflow obstruction[1]), to discourage such unconventional use, and to set the stage for further investigation regarding unconventional practice and ways of further clarifying its shortfalls or merits. In presenting this argument, we shall address several questions: (1) How frequently is augmentation therapy being prescribed for and used by heterozygous individuals today (hereafter called "unconventional use")? (2) What is the current evidence that heterozygous AAT deficiency predisposes to accelerated airflow obstruction, which is the main condition on which tenable use of augmentation therapy in this setting could be predicated? and (3) What information is needed to clarify the role of augmentation therapy, if any, for heterozygotes whose serum levels fall above the "protective threshold" value of 11 μmol?

How Frequently Is Augmentation Therapy Being Prescribed for and Used by Heterozygous Individuals Today?

Not surprisingly, systematic information regarding the frequency of unconventional augmentation therapy use is unavailable and prevalence estimates are understandably anecdotal. In preparing this commentary, we contacted the scientific and marketing leadership of all three current manufacturers of augmentation therapy and asked them to provide the total number of known instances of unconventional use. The two companies that responded explained the following: (1) these numbers are not available to them, (2) they do not promote or condone the use of augmentation therapy for individuals who are heterozygous for the AAT gene, and (3) they support the right of a physician to choose the therapy most appropriate for each patient under their care. That use of augmentation therapy for unconventional indications is clearly occurring currently is suggested by data from the Alpha-1 Foundation DNA and Tissue Bank, based at the University of Florida College of Medicine: of the 352 samples sent to the DNA bank with a PI*MZ genotype, 23 patients (6.5%) were receiving augmentation therapy at the

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All authors are members of the Alpha-1 Foundation Medical and Scientific Advisory Committee. Additional membership can be found at the Alpha-1 Foundation Web site (www.alphaone.org). Dr. Silverman is also a member of the Alpha-1 Foundation Board of Directors.

Dr. Sandhaus has presented talks relating to AAT deficiency at events sponsored by Talecris Biotherapeutics, CSL Behring, Baxter Healthcare, and Dey Pharmaceuticals, and has been a principal investigator for therapeutic clinical trials in AAT deficiency sponsored by Talecris Biotherapeutics, CSL Behring, and Kamada Pharmaceuticals. Dr. Turino has no conflicts of interest to disclose. Dr. Stocks has received compensation for serving on the advisory boards of, and has also been the recipient of research funding from, Bayer, Talecris, CSL Behring, Baxter, and Kamada for AAT drug development. In the past 3 years, Dr. Strange has consulted for Arriva, GTC Biotherapeutics, and CSL Behring, and is on the speaker's bureau for Talecris with total amounts of compensation less than US $10,000. He has held grants from Talecris, the Alpha-1 Foundation, Alpha-1 Association, and the National Institutes of Health for study of AAT deficiency. Dr. Trapnell has no conflicts of interest to disclose. Dr. Silverman received an honorarium for a talk on COPD genetics in 2006, grant support and consulting fees from GlaxoSmithKline for two studies of COPD genetics, an honorarium from Bayer Biologicals for a symposium at the 2005 European Respiratory Society Meeting, and an honorarium for a talk at the Lund Symposium in 2007 and consulting fees from AstraZeneca. Ms. Everett has severe AAT deficiency, receives augmentation therapy, and has been a member of the voluntary leadership of the Alpha-1 Foundation for the past 12 years. Dr. Stoller has served as a consultant to Talecris Biotherapeutics; has given lectures that have been supported by Talecris Biotherapeutics, Baxter Healthcare, Grifols, and CSL Behring; and has served as a member of data monitoring and safety committee for Kamada Pharmaceuticals.

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