



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 μ mol or approximately 50 mg/dL using nephelometry] is a common but under-recognized 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 societies¹ 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 year⁴).

The original dose-finding study⁵ 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 uncommon⁶), 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

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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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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 obstruction¹), 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

time of the DNA donation. The collective experience of the current members of MASAC and the Alpha-1 Foundation Clinical Resource Centers were polled and several cited awareness of instances in which PI*MZ heterozygotes were receiving augmentation therapy at the time of referral, often at the suggestion of a local pharmaceutical sales representative to a physician with little experience treating individuals with AAT deficiency. To the extent that response to this query was small ($n = 16$) and that knowledge by such members of unconventional practice is casual and anecdotal, this experience likely underestimates the total experience of using augmentation therapy for unconventional indications.

Even if infrequent, the potential adverse consequences of using augmentation therapy for unconventional indications warrant attention. In the context that current evidence provides no scientific rationale for such practice but that augmentation therapy is expensive, individuals receiving augmentation therapy for unconventional indications have significant expenditure of insurance coverage and threats to their insurance caps. As an example, for those with a \$1 million dollar cap, the costs of augmentation therapy alone could approach this cap in as few as 10 years, which well exceeds the duration since the first approved augmentation therapy drug became available in 1988. Erosion of the insurance cap could also threaten the recipient's ability to receive insurance coverage for other health-care needs, which are often numerous for individuals with COPD and common comorbidities.¹⁰ This insurance expenditure also compounds the personal co-pays that some individuals bear, further threatening resources needed to garner needed health care. In our view, both types of expenditure from this unconventional practice pose the ethical dilemma of threatening recipients' access to other needed treatment. Other potential adverse effects of this unconventional practice include exposure to the risk of receiving a pooled human plasma-derived agent, albeit small,⁶ as well as potential erosion of drug supply, which has been a problem for the augmentation therapy-receiving community in the past. Taken together, we contend that the risks outlined above caused by the current practice of using augmentation therapy for PI*MZ heterozygotes greatly outweigh any potential or hoped-for benefits and, absent of evidence challenging current understanding, should be absolutely discouraged.

WHAT IS THE CURRENT EVIDENCE THAT HETEROZYGOUS AAT DEFICIENCY PREDISPOSES TO ACCELERATED AIRFLOW OBSTRUCTION?

Another related question regards the evidence that PI*MZ heterozygotes are at risk for accelerated

airflow obstruction compared with AAT-replete individuals. Many studies have approached this question, but the results have been quite disparate. In a metaanalysis of available well-designed studies, Hersh et al¹¹ found no significant risk for reduced FEV₁ in cross-sectional population-based studies comparing PI*MZ to PI*MM individuals; however, an increased odds ratio (2.3) for COPD was found in case-control studies comparing the prevalence of the PI*MZ genotype in COPD and control subjects. Potential explanations for these findings include a very slight increased risk of lung disease in all individuals with the PI*MZ genotype or a substantial risk in a subgroup of individuals with this genotype. However, it is not currently possible to identify PI*MZ subjects who are at increased risk for COPD, although this is an important area for future research.

A longitudinal study¹² of lung function in PI*MZ individuals showed a very small (25 mL/yr vs 21 mL/yr) but statistically significant acceleration of decline of FEV₁ compared with individuals with normal AAT levels. We regard this small difference as clinically insignificant and not warranting consideration of augmentation therapy and believe, based on our conversations with colleagues, that most clinicians concur. Of note, individuals with the even more common AAT heterozygote PI*MS are even less likely to be at increased risk of lung disease because AAT blood and lung levels of these individuals tend to be close to or within the normal range.

WHAT INFORMATION IS NEEDED TO CLARIFY THE ROLE OF AUGMENTATION THERAPY FOR HETEROZYGOES WHOSE SERUM LEVELS FALL ABOVE THE PROTECTIVE THRESHOLD VALUE OF 11 μ MOL?

In the context that current evidence demonstrating a clinically significant acceleration of lung function decline in PI*MZ heterozygotes is sparse, augmentation therapy seems unlikely to hold great promise for most PI*MZ heterozygotes. That said, many clinicians with significant AAT experience cite at least a few instances of PI*MZ individuals who have severe airflow obstruction despite never having smoked. As such, the first needed inquiry would be to clarify the prevalence of these "rapidly accelerated decliners" among all PI*MZ individuals in order to identify a cohort that is potentially amenable to further study. Next, in keeping with the lines of evidence by which the efficacy of augmentation therapy has been judged to date and by which available drugs have achieved US Food and Drug Administration approval, endorsing the use of augmentation therapy for this (presumably small) subset of rapidly declining PI*MZ

heterozygotes would require demonstrating, ideally in a randomized controlled trial, that receipt of augmentation therapy slows the development of emphysema and its sequelae, whether by measuring lung function, lung density on CT, functional status, COPD-attributed morbidity, and/or survival. While we cannot completely discount the feasibility of such research, the challenges of identifying a subset of rapidly accelerating PI*MZ heterozygotes and then enlisting this subset in a prospective trial seem daunting. On this basis, we regard the prospects of demonstrating the benefit of currently “unconventional” indications to be very dim.

Physicians legally enjoy the privilege of being able to prescribe medications for indications that have not been Food and Drug Administration approved. In return, their patients and society benefit from the development of new therapeutic options for older drugs and, at least in theory, some competitive pressure on medication costs. However, the media and the general population poorly understand and are occasionally alarmed by the concept of using medications for “unapproved” indications, and this prescriber privilege may become endangered if drugs are prescribed unreasonably or without some rational basis for expecting patient benefit.

Overall, the absence of available evidence (or even compelling suspicion) that administering AAT augmentation therapy to individuals with AAT serum levels above the protective threshold value of 11 μmol confers benefit, coupled with concerns of adverse effects, both clinical and economic, of this practice leads the members of MASAC to discourage current use of augmentation therapy for such unconventional indications in the strongest terms. While we certainly applaud and would welcome the clarity that might come from concerted study, we recognize that impediments to rigorously studying this issue are substantial. Pending the availability of compelling evidence to support this practice, we call for the following: (1) clinicians should avoid prescribing augmentation therapy for PI*MZ heterozygotes and consider referral of such patients to specialists with

experience in treating AAT deficiency; (2) the insurance industry should closely evaluate reimbursing for such unconventional indications; and (3) the US Food and Drug Administration should clarify and reconcile the package inserts of all these augmentation therapies to discourage this practice.

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