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EDITORIAL

Alpha-1 Antitrypsin Deficiency: Doing the Right Thing (or Start Kissing Those Frogs)

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The article by de Serres et al. (1) adds additional volume to the voices already calling for alpha-1 antitrypsin (AAT) testing of all individuals with chronic obstructive pulmonary disease (COPD). These authors join the American Thoracic Society, the American College of Chest Physicians, the European Respiratory Society, the World Health Organization, and the American Association for Respiratory Care in endorsing this recommendation, stated most directly in the *ATS/ERS Standards for the Diagnosis and Management of Individuals with Alpha-1 Antitrypsin Deficiency* (2). While everyone seems to agree that all individuals with COPD should be tested for AAT deficiency, no one seems to be doing it!

Some may disagree with de Serres et al. when they include low risk and heterozygote phenotypes as AAT deficient. Even limiting the definition of AAT deficiency to the most severely deficient phenotypes leaves us with an expected prevalence of between one and two percent of the COPD population based on recent screenings of this population. These same data mean that practicing physicians will find many negative test results in their inbox before identifying that unexpected AAT deficient COPD patient. The treatment of that one patient will be dramatically changed by that identification. You have to kiss a lot of frogs to find a prince (or princess).

Having worked diligently to identify the one, two, or six patients in a given practice with COPD and undetected AAT deficiency, the next step is often the initiation of intravenous augmentation therapy employing human plasma-derived AAT concentrate. Some still question the effectiveness of this therapy, but the overwhelming preponderance of evidence confirms the success of this approach. Studies have demonstrated improvements in survival, exacerbation events, and rate of decline of FEV_1. Individuals with COPD and AAT deficiency should certainly be considered for this therapy, especially if they have demonstrated accelerated decline in lung function.

For nearly two decades there was only a single marketed augmentation therapy available: Prolastin®. This was initially marketed by Cutter Laboratories, then Miles, Bayer Biologicals, and now Talecris Biotherapeutics. In 2003 and 2004, two additional products were introduced: Aralast® (initially developed by Alpha Therapeutics and now marketed by Baxter Healthcare) and Zemaira® (initially developed by Armour, then Centeon, Aventis Behring, and now marketed by ZLB Behring). In addition, Trypsone from Grifols is available in Europe. The newer products in the United States were approved by the Food and Drug Administration (FDA) based on relatively small studies (each fewer than 50 subjects) documenting that each newer product was not inferior to Prolastin in either safety or biological AAT levels attained.

In spite of the pure non-inferiority methodology used to evaluate these newer products, there is an ongoing battle of words among all three manufacturers and their representatives claiming clinical advantages of various sorts. In fact, there are differences in the formulations and even in the biochemical nature of these products. But, to date, no study has demonstrated any clinical differences. Similarly, there have been no studies evaluating the potential for any short- or long-term safety differences among the products. Most physicians who treat patients with AAT deficiency rely on distinctions in cost, the attractiveness of drug representatives, and the whims of insurers when deciding which product to prescribe.

Augmentation therapy is only one aspect of the comprehensive management of individuals with lung disease due to AAT deficiency. For example, thousands of AAT deficient patients on augmentation therapy are followed by AlphaNet, a not-for-profit, patient-driven disease management organization that generates funding for various research and patient activities within the AAT deficiency community. AlphaNet's self-management program has been documented to provide improvements in the quality of life and the healthcare utilization patterns of individuals with AAT deficiency.

Patients are followed by AlphaNet's program and its regional disease management coordinators, all of whom are specially

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trained individuals who themselves have AAT deficiency. Patients in this disease management program have demonstrated improvements in St. George Respiratory Questionnaire and SF-36 scores, fewer unscheduled healthcare encounters, fewer exacerbations, and more appropriate medication usage comparing each patient with the year prior to enrolling in the program.

One additional issue needs to be addressed with respect to augmentation therapy. With the known formulation differences between products, the small preapproval safety studies, and a widely dispersed patient population receiving these drugs, it behooves us to ensure that post-marketing safety surveillance is scrupulously performed. For those already treating patients with augmentation therapy, make certain to report any side effects or adverse events associated with drug administration either to the manufacturer or to the FDA using their MedWatch form (www.fda.gov/medwatch).

Identification, treatment, and monitoring—following these three tenets can improve the lives of individuals with COPD due to AAT deficiency. And keep kissing those frogs.

REFERENCES

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