

## $\alpha_1$ -Antitrypsin deficiency

### *Forgotten etiology*

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This review of one of the most common inherited conditions,  $\alpha_1$ -antitrypsin deficiency (AATD), will discuss the diagnosis and management of patients with this condition. A diagnosis of AATD should be considered in patients with premature or aggressive chronic obstructive pulmonary disease (COPD) or patients with nonresolving respiratory issues. Treatment consists of managing the patient's COPD and instituting  $\alpha_1$ -antitrypsin (AAT) augmentation therapy to slow the progression of loss of lung function. Family physicians care for most patients with respiratory disease and as such are perfectly suited to consider and confirm diagnosis of AATD, which currently is usually diagnosed fairly late in the course of illness.

#### Sources of information

Previously published guidelines and the medical literature about AATD and AAT augmentation were reviewed. The information presented here is based on available published literature that was obtained by searching PubMed, the Cochrane Library databases, and the reference lists of relevant articles. The searches were limited to English-language articles published between 1990 and 2009. The following search terms were used:  *$\alpha_1$ -antitrypsin deficiency*,  *$\alpha_1$ -antitrypsin augmentation therapy*, *efficacy*, *randomized controlled trial*, *observational study*, and *retrospective cohort study*. National and international respiratory guidelines were reviewed for recommendations about which patients to test for AATD. All studies of augmentation therapy were reviewed; they varied considerably in terms of study design, data collection, and analysis. The details of each study are listed in **Table 1**.<sup>1-6</sup> Levels of evidence were graded in accordance with recommendations from the University of Oxford's Centre for Evidence-Based Medicine (**Table 2**).<sup>7</sup>

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#### Abstract

**OBJECTIVE** To provide a review of  $\alpha_1$ -antitrypsin deficiency (AATD),  $\alpha_1$ -antitrypsin (AAT) augmentation, and the recommendations for timely recognition and treatment.

**SOURCES OF INFORMATION** Published guidelines and the medical literature about AATD and AAT augmentation were reviewed. The information presented is based on available published literature obtained by searching PubMed, the Cochrane Library databases, and the reference lists of relevant articles. Searches were limited to English-language articles published between 1990 and 2009.

**MAIN MESSAGE**  $\alpha_1$ -Antitrypsin deficiency, a genetic disorder characterized by low serum levels of AAT, predisposes affected patients to development of early-onset pulmonary disease (most commonly emphysema and chronic obstructive pulmonary disease) and occasionally even life-threatening liver disease. Despite being one of the most common inherited conditions (affecting about 1 in 2000 to 5000 people), AATD is underrecognized. This is unfortunate; although there is no cure for AATD, prompt diagnosis can help impede loss of lung function. Specific treatment of this deficiency with augmentation therapy is effective.

**CONCLUSION**  $\alpha_1$ -Antitrypsin deficiency is a common genetic condition that can be involved in premature lung and liver disease. Consider the diagnosis to allow earlier institution of AAT augmentation therapy to slow the progression of premature lung disease in affected patients.

#### Résumé

**OBJECTIF** Faire le point sur le déficit en  $\alpha_1$ -antitrypsine (DAAT), le traitement substitutif à l' $\alpha_1$ -antitrypsine (AAT) et les recommandations pour un dépistage et un traitement précoces.

**SOURCE DE L'INFORMATION** On a consulté les directives publiées ainsi que la littérature médicale sur le DAAT et le traitement substitutif à l'AAT. L'information présentée ici provient d'une recherche de la littérature existante dans PubMed et dans les bases de données de Cochrane Library, en plus de la bibliographie d'articles pertinents. On s'est limité aux articles de langue anglaise parus entre 1990 et 2009.

**PRINCIPAL MESSAGE** Le DAAT, une affection génétique caractérisée par un bas niveau d'AAT, prédispose les sujets atteints à des maladies pulmonaires précoces (généralement l'emphysème ou une maladie pulmonaire obstructive chronique) et parfois à une maladie hépatique potentiellement mortelle. Même s'il s'agit de l'une des maladies héréditaires les plus fréquentes (environ une personne sur 2000 à 5000), le DAAT est malheureusement sous-diagnostiqué. Cette maladie est incurable, mais un diagnostic précoce peut prévenir la perte de la fonction pulmonaire. Il existe un traitement spécifique de ce déficit par thérapie substitutive.

**CONCLUSION** Le DAAT est une affection génétique fréquente qui peut contribuer à une maladie pulmonaire ou hépatique précoce. On doit penser à ce diagnostic si on veut instituer un traitement substitutif précoce à l'AAT et ainsi ralentir la progression d'une maladie pulmonaire prématurée chez les sujets atteints.

**Table 1. Published studies of AAT augmentation therapy**

STUDY	STUDY DESIGN	TREATMENT PROTOCOL	OUTCOME	LEVEL OF EVIDENCE
Seersholm et al, <sup>1</sup> 1997	Observational, nonrandomized study; comparison of rate of change in FEV <sub>1</sub> in treated German patients vs untreated Danish patients	Weekly AAT therapy, 60 mg/kg	Significant difference in rate of decline in FEV <sub>1</sub> between the groups ( $P=.02$ ): treated German patients 53 mL/y vs untreated Danish patients 75 mL/y; difference of 22 mL/y	II
AATD Registry Study Group, <sup>2</sup> 1998	Observational, nonrandomized study	AAT therapy, 60 mg/kg (51% weekly, 25% biweekly, 22% monthly)	Significantly lower rate of FEV <sub>1</sub> decline (mean difference 27 mL/y) in treated patients with FEV <sub>1</sub> at 35% to 49% of predicted value ( $P=.03$ ); decreased mortality in treated group ( $P=.02$ )	II
Dirksen et al, <sup>3</sup> 1999	Randomized controlled trial	Every 4 wk, AAT therapy (250 mg/kg) or placebo (albumin, 625 mg/kg)	Nonsignificant difference in loss of lung tissue between groups: placebo group 2.6 g/L/y vs treated group 1.5 g/L/y ( $P=.07$ )	I
Lieberman, <sup>4</sup> 2000	Observational, Web-based survey	AAT therapy, 60 mg/kg/wk (54% weekly, 35% biweekly, 7% monthly)	Number of lung infections decreased from 3-5/y pretreatment to 0-1/y posttreatment ( $P<.001$ )	II
Wencker et al, <sup>5</sup> 2001	Multicentre, retrospective cohort study; comparison of rate of FEV <sub>1</sub> decline before and after treatment	Weekly AAT therapy, 60 mg/kg	Significant difference in rate of FEV <sub>1</sub> decline: 49.2 mL/y pretreatment vs 34.2 mL/y posttreatment ( $P=.019$ )	II
Dirksen et al, <sup>6</sup> 2009	Randomized, multicenter, double-blind, placebo-controlled, parallel-group	Weekly, AAT therapy (60 mg/kg) or placebo (2% albumin)	CT is a more sensitive outcome measure of emphysema-modifying therapy than physiology and health status; a trend toward treatment benefit from AAT augmentation therapy was demonstrated	I

AAT— $\alpha_1$ -antitrypsin, AATD— $\alpha_1$ -antitrypsin deficiency, CT—computed tomography, FEV<sub>1</sub>—forced expiratory volume of air in 1 second.

**Table 2. Classification of levels of evidence**

LEVEL	TYPES OF EVIDENCE
I	High-quality RCT with statistically significant difference or no statistically significant difference but narrow CIs Systematic review of level I RCTs (and study results were homogenous)
II	Lower-quality RCT (eg, <80% follow-up, no blinding, or improper randomization) Prospective comparative study Individual cohort study Systematic review of level II studies or level I studies with inconsistent results
III	Case-control study Retrospective comparative study Systematic review of level III studies
IV	Case series
V	Expert opinion

CI—confidence interval, RCT—randomized controlled trial. Adapted from the Oxford University Centre for Evidence-Based Medicine.<sup>7</sup>

### Case

John is a 39-year-old man who has been developing worsening shortness of breath for the past few years. He has a cough, which he calls his “smoker’s cough,” and he will often cough up a bit of sputum. He admits to smoking about a pack a day for the past 5 years, up from the half a pack a day he had smoked since about age 15. You suspect he could have asthma or COPD and send him for spirometry, which shows that he has obstruction, with a ratio of 60% and a forced expiratory volume of air in 1 second (FEV<sub>1</sub>) of only 65% of the predicted value. There is no difference in his lung function after administration of bronchodilators, even though this test is conducted when he is symptomatic. You come to the conclusion (correctly) that he has COPD. His father had emphysema, so John is familiar with the problem and agrees to stop smoking. He feels somewhat better when he starts taking tiotropium, and salbutamol as required, and you give him the pneumococcal vaccine and the flu shot. You have done a great job, but is there something you might have missed?

## Background and history

$\alpha_1$ -Antitrypsin deficiency is a genetic disorder characterized by low serum levels of AAT. Low plasma and alveolar concentrations of AAT in the human body predispose individuals to development of early-onset pulmonary disease, most commonly emphysema and COPD. Life-threatening liver disease is another possible consequence of AATD. Although it is one of the most common inherited conditions—it affects about 1 in 2000 to 5000 individuals—it is underrecognized.<sup>8</sup> It is estimated that only about 5% of patients with AATD in the United States have been properly diagnosed; therefore, most affected patients are unaware that they could benefit from healthier lifestyle changes (such as smoking cessation) or from the specific therapy that is available.<sup>9</sup>

The understanding of AATD has evolved since it was initially discovered in the early 1960s by Laurell and Eriksson<sup>10</sup> as the cause of familial emphysema.  $\alpha_1$ -Antitrypsin is synthesized primarily by the liver then released into the bloodstream, ultimately to protect the lungs by blocking the effects of neutrophil elastase (NE). Neutrophil elastase is secreted by neutrophils in response to infection or irritants in order to digest damaged tissue in the lungs.  $\alpha_1$ -Antitrypsin binds to the excess NE, which results in inactivation of the protease. Sometimes a gene mutation produces an abnormal form of the AAT protein that cannot be released from the liver, which means it cannot enter the bloodstream. Without the protection provided by this protein, the lungs are left vulnerable to attack by NE. Conversely, accumulation of excess AAT in the liver can lead to cellular congestion and destruction, with possible development of severe liver disease and organ failure.<sup>11</sup>

## Genetics and AAT plasma levels

More than 100 different genetic variants of AAT have been identified. Differences in the speed of migration on gel electrophoresis have been used to identify the protein variants. Normal individuals are homozygous for the M variant ( $Pi^*M/Pi^*M$ ) and have AAT serum concentrations between 20 and 53  $\mu\text{mol/L}$ ; other genotypes lead to reduced levels of AAT. The S allele produces moderately low levels of this enzyme, and the Z allele produces very little AAT. Most individuals affected by a clinically significant deficiency have some combination of the 2 abnormal alleles. In individuals with Pi SS, Pi MZ, or Pi SZ phenotypes, blood levels of AAT are reduced to 40% to 60% of normal levels. The most common form of severe AAT deficiency occurs in those homozygous for the Z allele ( $Pi^*Z/Pi^*Z$ ). Serum levels of AAT in these patients are about 3.4 to 7  $\mu\text{mol/L}$ —10% to 15% of normal serum levels. The protective threshold in serum levels has been identified as 11  $\mu\text{mol/L}$ . Emphysema develops in most (but not all) individuals with serum levels below 9  $\mu\text{mol/L}$ .<sup>12</sup> Homozygotes for

the Z allele account for approximately 95% of cases of clinically recognized AATD.<sup>13</sup>

## Epidemiology

$\alpha_1$ -Antitrypsin deficiency is a common hereditary disorder affecting individuals in almost all regions of the world, including North America, Europe, the Middle East, Africa, Asia, and Australia.  $\alpha_1$ -Antitrypsin deficiency has been identified in all populations, but it is most common in individuals of Northern European and Iberian descent. Rates found among white people are similar worldwide, with an estimated 117 million carriers and 3.4 million affected individuals.<sup>14</sup> If the estimated 19.3 million white COPD patients in the United States were tested for AATD, it is predicted that approximately 1.29 million new patients would be identified.<sup>14</sup> This number includes severely deficient individuals in addition to carriers. Despite this prevalence, AATD is still largely undetected and underdiagnosed by health care providers.<sup>9</sup> The results presented by de Serres and colleagues in 2006 suggest that targeted screening for AATD should be implemented in countries with large populations of white COPD patients.<sup>14</sup> One of the main challenges for physicians is that AATD can cause similar respiratory symptoms to those seen in asthma or COPD. The earliest symptoms include shortness of breath, cough, excess sputum production, reduced ability to exercise, and wheezing. Symptoms can initially be sporadic; however, if wheezing is the main symptom, individuals are often diagnosed with asthma. Smoking or exposure to tobacco smoke accelerates the appearance of symptoms and damage to the lungs.

## Management of AATD

Although there is no cure for AATD, early diagnosis remains important because affected patients can modify their lifestyle choices to reduce the risk of emphysema and they can benefit from the effective therapy that is available. Treatment can include smoking cessation,

### Box 1. Who should you consider testing for $\alpha_1$ -antitrypsin deficiency?

Consider testing patients with the following conditions:

- COPD that remains symptomatic despite bronchodilator therapy
- emphysema
- asthma with airflow obstruction that is not completely reversible
- unexplained liver disease

You might also consider testing the following patients:

- asymptomatic patients with both persistent obstruction on pulmonary function tests and risk factors for the disorder (eg, smoking)

COPD—chronic obstructive pulmonary disease.

Data from the American Thoracic Society and the European Respiratory Society.<sup>12</sup>

inhaled bronchodilators, corticosteroids, and supplemental oxygen. The only specific therapy for AATD is augmentation therapy, which is administration of exogenous protease inhibitors in the form of pooled human plasma AAT. The aim of augmentation therapy is to restore the level of circulating AAT (ie, to raise and maintain serum levels above the protective threshold of 11  $\mu\text{mol/L}$ ) and thus arrest the course of the disease and halt any further damage to the lungs. There are currently 4 different commercially available purified pooled human plasma-derived AAT products that are licensed in several countries: Prolastin (Talecris Biotherapeutics), Aralast (Baxter), Zemaira (CSL Behring), and Trypsone (Probitas Pharma). Since 1988, only Prolastin has received regulatory approval in Canada.

Various studies have evaluated the effects of augmentation therapy, including several observational cohort studies with concurrent or historical controls<sup>1,2,4,5</sup> and, until recently, a single small randomized controlled trial<sup>3</sup> (Table 1<sup>1-6</sup>).

The largest observational cohort study (level II evidence) was conducted by the US National Heart, Lung and Blood Institute (NHLBI).<sup>2</sup> In 1988 the NHLBI established a registry for individuals with severe deficiency of AAT as a means of collecting information on the natural history of AATD. In 1998 the NHLBI published data derived from 1048 patients who were followed for 3.5 to 7 years. Among all subjects receiving augmentation therapy (continuously or intermittently) no difference in FEV<sub>1</sub> decline was detected; however, among patients with FEV<sub>1</sub> values at 35% to 49% of the predicted values, FEV<sub>1</sub> decline slowed significantly for subjects receiving therapy (mean difference 27 mL/year;  $P=.03$ ) compared with those not receiving therapy. Further, patients receiving augmentation therapy had a 36% reduction in mortality compared with patients not receiving therapy ( $P=.02$ ). The study was not randomized, so the differences favouring augmentation therapy might have been the result of other factors, such as smoking habits (more current smokers) and socioeconomic status (lower income and less insurance coverage), factors for which researchers could not control.

Lieberman addressed the question of clinical efficacy by conducting a Web-based survey of patients with the Pi ZZ phenotype who were not receiving therapy compared with patients who had received augmentation therapy for 1 to 10 years (level II evidence).<sup>4</sup> The results of this study, derived from the responses of 143 patients (96 receiving therapy; 47 not receiving therapy), suggest that augmentation therapy is associated with a significant reduction in the frequency and severity of lung infections in patients with AAT-related emphysema. Before starting augmentation therapy most patients reported a frequency of 3 to 5 infections per year; this number dropped to 0 to 1 infections per year while receiving therapy ( $P<.001$ ). Further, 55% of

untreated patients experienced more than 2 infections per year compared with 18% of patients receiving therapy ( $P<.001$ ).

A more recent multicentre, retrospective cohort study evaluating augmentation therapy was conducted by Wencker and colleagues (level II evidence).<sup>5</sup> The progress of emphysema was evaluated in 96 patients with severe AATD before and after receiving weekly AAT augmentation therapy. Lung function tests were conducted for a minimum of 12 months, both before and after therapy. This was the first study comparing lung function before the introduction of augmentation therapy with lung function after treatment in the same individuals. The overall rate of FEV<sub>1</sub> decline after initiation of augmentation therapy was significantly lower than the rate of decline before therapy (34.2 mL/year vs 49.2 mL/year;  $P=.019$ ). The highest reduction in the decline in FEV<sub>1</sub> was observed in patients who had a rapid decline in FEV<sub>1</sub> before initiation of augmentation therapy. Furthermore, even patients with FEV<sub>1</sub> more than 65% of predicted values had a large and significant reduction in decline in FEV<sub>1</sub> of 73.6 mL/year after augmentation therapy ( $P=.045$ ). The reported decline in FEV<sub>1</sub> is similar to the reduction previously reported.<sup>1,2</sup>

The first randomized, parallel, double-blind, controlled trial comparing augmentation therapy to placebo in Pi ZZ phenotype ex-smokers with moderate emphysema was published in 1999 (level I evidence).<sup>3</sup> Twenty-six patients from the Danish Alpha-1-Antitrypsin Deficiency Registry and 32 patients from a similar Dutch registry participated. Patients were randomized to receive monthly infusions of either AAT therapy or albumin over a period of 3 years. Two Dutch subjects dropped out of the study during the first 2 years because they resumed smoking; their data were omitted from further analyses. The rates of FEV<sub>1</sub> decline using both laboratory-based spirometry and daily home spirometry measurements showed no difference between the treated and control groups. Unfortunately, this study did not have enough power to show a statistically significant effect of augmentation therapy on preventing the continuous decline of lung function compared with placebo. However, assessment of lung densitometry by chest computed tomography (CT) scans showed a nearly significant trend favouring a slower progression of emphysema in the augmentation therapy group ( $P=.07$ ).

Recently, a European randomized, multicentre, double-blind, placebo-controlled, parallel-group study was published (level I evidence).<sup>6</sup> This study investigated novel outcome measures to determine the effects of augmentation therapy on emphysema progression in AATD patients. A total of 77 patients with AATD were randomized to receive either weekly infusions (60 mg/kg) of AAT therapy or placebo (2% albumin) for 2 to 2.5 years. The primary end points were frequency of exacerbations and progression of emphysema as assessed by CT lung

## EDITOR'S KEY POINTS

- $\alpha_1$ -Antitrypsin deficiency (AATD) is a genetic disorder characterized by low serum levels of  $\alpha_1$ -antitrypsin (AAT). Low plasma and alveolar concentrations of AAT in the human body predispose individuals to development of early-onset pulmonary disease, most commonly emphysema and chronic obstructive pulmonary disease.
- Only approximately 5% of patients with AATD in the United States have been properly diagnosed. Diagnosis of AATD should be considered in patients with premature or aggressive chronic obstructive pulmonary disease or patients with nonresolving respiratory issues.
- The only specific therapy for AATD is augmentation therapy—administration of exogenous protease inhibitors in the form of pooled human plasma-derived AAT. Such therapy is now recommended for patients with forced expiratory volume of air in 1 second (FEV<sub>1</sub>) values between 35% and 65% of their predicted FEV<sub>1</sub> values, particularly those who have quit smoking and have still experienced a rapid decline in FEV<sub>1</sub>.

## POINTS DE REPÈRE DU RÉDACTEUR

- Le déficit en  $\alpha_1$ -antitrypsine (DAAT) est une affection génétique caractérisée par un bas niveau sérique d' $\alpha_1$ -antitrypsine (AAT). Les faibles concentrations plasmatiques et alvéolaires d'AAT prédisposent les sujets à développer précocement des maladies pulmonaires, habituellement l'emphysème ou une maladie pulmonaire obstructive chronique (MPOC).
- Aux États-Unis, à peine 5% environ des patients atteints de DAAT ont été diagnostiqués correctement. On devrait penser à ce diagnostic chez tout patient présentant une MPOC précoce ou agressive, ou chez ceux qui ont des problèmes respiratoires persistants.
- Le seul traitement spécifique du DAAT est la thérapie substitutive – administration d'inhibiteurs exogènes de la protéase sous la forme d'AAT extrait d'un pool de plasma humain. Ce traitement est maintenant recommandé pour les patients dont le volume expiratoire maximal par seconde (VEMS) est entre 35 et 65% de la valeur prédite, particulièrement chez ceux qui ont cessé de fumer et qui continuent d'avoir une baisse rapide du VEMS.

density measurement. The authors concluded that CT densitometry is a sensitive measure of the loss of lung tissue. Lung density decline was lower with augmentation therapy compared with placebo at all time points (*P* values for treatment difference ranged from .049 to .084), suggesting a beneficial treatment response to augmentation therapy.

Taken as a whole, the results of the published studies have shown that augmentation therapy is associated with impeded rates of decline of lung function and fewer lung infections.

## Guidelines

In 2001, the Canadian Thoracic Society published a position statement on AATD.<sup>15</sup> In view of the data available, and owing to the limited supply of AAT available for augmentation therapy, the authors recommended reserving AAT augmentation therapy for AAT-deficient patients who had FEV<sub>1</sub> values at 35% to 50% of their predicted values, who had quit smoking, and who were taking optimal medical therapy yet continued to show rapid decline in FEV<sub>1</sub>. They also recommended that all AATD patients participate in the Canadian AAT Registry.

In 2005 the same authors revised their recommendations<sup>16</sup> because the limitations on the supply of AAT available had been alleviated as a result of increased production. Augmentation therapy is now recommended for individuals with FEV<sub>1</sub> between 35% and 65% of predicted values, who have quit smoking and still have rapid decline in FEV<sub>1</sub>. Augmentation therapy is also recommended for treating the rare null homozygotes, because these individuals have no detectable AAT and are more likely to have accelerated decline in lung function than Pi ZZ patients are.

In 2003, joint guidelines for the diagnosis and management of individuals with AATD from the American Thoracic Society and the European Respiratory Society were published.<sup>12</sup> They recommended that a single quantitative test for AAT should be performed on all individuals with COPD who remained symptomatic despite bronchodilator therapy, individuals with emphysema, those who had asthma with airflow obstruction that was not completely reversible, and those with unexplained liver disease. They also recommended testing asymptomatic patients with both persistent airflow obstruction on pulmonary function tests and risk factors (eg, smoking) for the disorder (**Box 1**<sup>12</sup>). Other advanced testing is usually not necessary.<sup>17</sup>

## Challenges

Despite these guideline recommendations there has been no improvement in the time taken to diagnose AATD; moreover, it appears that the disease is still largely undetected or misdiagnosed. Enhanced awareness of the disorder among health care providers should result in better management of AATD patients. Results


of a patient survey showed that the average age of diagnosis for AATD patients was 45.5 years, and the average interval between onset of symptoms and diagnosis was 8.3 years.<sup>9</sup> Most unrecognized AATD occurs among those with COPD; as primary care physicians treat many of these patients, primary care physicians can play an important role in identifying and improving the management of AATD.

## Case resolution

You send John for testing for AATD. His blood test results show that his AAT levels are low, and further testing shows that he is a Pi ZZ subtype. You refer him to a respirologist with an interest in AATD, and he is treated with augmentation therapy. Your note from the specialist congratulates you for making such an astute diagnosis. John's family is also tested, which is of particular importance for his 15-year-old son, who—you guessed it—has just started smoking.

## Conclusion

$\alpha_1$ -Antitrypsin deficiency is a common genetic condition

that can be involved in premature lung and liver disease. Consider the diagnosis to allow for appropriate lifestyle changes and earlier institution of augmentation therapy to slow the progression of premature lung disease in afflicted in patients. 

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### Contributors

**Dr Kaplan** identified the topic, participated in the literature search, drafted the article, reviewed all edits, and approved the final article for publication. **Dr Cosentino** participated in the literature search and helped to revise the article before its final approval.

### Competing interests

**Dr Kaplan** was a member of the Talecris Biotherapeutics  $\alpha_1$ -antitrypsin deficiency advisory board. He did not receive any funding for writing this article. Assistance was given by Talecris staff in providing the studies that have been described. He is also a member of an advisory board for, or has received honoraria from, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Merck Frosst, Novartis, Nycomed, Pfizer, and Purdue. **Dr Cosentino** is an employee of Talecris Biotherapeutics, makers of Prolastin.

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