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How are we in Brazil with the treatment of alpha-1 antitrypsin deficiency?

Maria Vera Cruz de Oliveira Castellano[1], Paulo Henrique Feitosa[2]

TO THE EDITOR,

Recently, the Brazilian Journal of Pulmonary Medicine published a review article on alpha-1 antitrypsin deficiency (AATD),[1] which addresses the diagnosis and future prospects for reducing underdiagnosis in Brazil. However, the treatment is as important as the diagnosis, and, in this aspect, there is still a lot to be done.

AAT deficiency is a rare disease that is associated with early-onset pulmonary emphysema and various forms of hepatic disease, such as cirrhosis and neonatal liver disease.

Smoking has been shown to be a risk factor for the development of emphysema in individuals with AATD. Therefore, it is important to prevent smoking initiation, as well as promote smoking cessation in current smokers with AATD.[1]

The treatment for pulmonary disease associated with AATD is the same as that recommended for COPD, according to consensus and guidelines, and, when indicated, replacement therapy with AAT must be performed.

The discovery of the structure and function of the AAT protein (neutrophil protease inhibitor, potent anti-inflammatory, and immunoregulator) and its production from human plasma has allowed for replacement therapy to prevent the progression of emphysema.[2] The goal of treatment is to elevate serum AAT levels, maintain the concentration in the pulmonary interstitium above the "protective threshold", and slow the progression of emphysema. The concentration of anti-neutrophil elastase obtained from bronchoalveolar lavage fluid in patients with AAT deficiency after replacement therapy increases by 70% compared to baseline levels. This therapy was approved by the FDA in 1987 after studies evidenced its biochemical efficacy.[2]

Following diagnosis, it is important that the patient have access to replacement therapy. For this to occur, knowledge of pharmacological and technical aspects and its availability in countries as heterogeneous as Brazil are necessary.

Replacement therapy is indicated for non-smokers or former smokers over 18, with genetic variants of AAT compatible with deficiency, reduced serum AAT levels (< 116 mg/dL), and evidence of airflow limitation upon spirometry. Most patients with the PI*ZZ genotype or PI*Z null variants have serum levels < 57 mg/dL (nephelometry); it can be stated that serum levels < 20% of the normal value are suggestive of PI*ZZ deficiency.[3] Patients with other genetic variants may also present reduced serum AAT levels and an indication for replacement therapy. Heterozygous individuals (PI*MZ or PI*MS) usually are not candidates for AAT replacement since they do not have an increased risk of emphysema if non-smoking.[4]

The GOLD guidelines suggest that patients with an indication for AAT replacement are those with FEV1 of 35% to 65% of the predicted values (Evidence B).[5] The rationale for selecting this FEV1 range is that not all patients with AATD will progress with rapid loss of lung function, especially after smoking cessation. The American/European consensus[3] on AAT deficiency, after evaluating studies with mortality and FEV1 outcomes in patients who received replacement therapy compared to those who did not, concluded that the indication should occur with FEV1 between 31% and 65% of the predicted values. The Canadian guidelines[6] indicate AAT replacement for patients diagnosed with COPD (FEV1 between 25-80% of the predicted values) under maximal pharmacological and non-pharmacological therapy (*e.g.*, pulmonary rehabilitation) and justify this conclusion through the benefits of pulmonary density preservation, assessed by computed tomography (Evidence B) and decreased mortality (Evidence C).

In a cohort of 139 patients, pulmonary density was analyzed by computed tomography, and it was confirmed that treatment with AAT prevented the progression of emphysema in patients with AATD.[7] Another study[8] concluded that patients receiving AAT presented fewer exacerbations and lower levels of C-reactive protein, IL-6, IL-8, and TNFα.

The main objective of AAT replacement treatment is to contain the destruction of the lung parenchyma caused by the protease/antiprotease imbalance, which justifies, in some cases, the initiation of treatment in patients with mild to moderate degrees of airflow obstruction. It is important to remember that chest tomography to assess pulmonary density is more sensitive than spirometry for monitoring these patients. Moreover, it is essential that, in addition to spirometry, diffusion of carbon monoxide (DLCO), lung volumes, quality of life questionnaires, COPD assessment tests, and exacerbations are periodically evaluated to detect the benefits of replacement therapy and potential clinical worsening.

Treatment with intravenous AAT replacement has technical specifications and is recommended to be applied in Reference Centers, Primary Care Units, or Infusion Centers with trained staff. AAT must be transported and stored at low temperatures, and the recommended dose is 60 mg/kg of body weight weekly. Adverse reactions

1. Serviço de Pneumologia, Hospital do Servidor Público Estadual de São Paulo, São Paulo (SP), Brasil.
2. Serviço de Pneumologia, Hospital Regional da Asa Norte, Brasília (DF), Brasil.

are rare and mild and include fever, dyspnea, tremors, and headache. There are no reports of hepatitis or HIV transmission upon AAT treatment.[9] The intravenous AATs are supplied as lyophilized powder or in liquid form. Instructions for reconstituting the lyophilized powder are labeled on the package insert and must be strictly followed. After reconstitution, the AAT injection must be given within three hours.

There are currently eleven countries in which AAT is provided through federal public protocols: Canada and the USA since 1988, Germany and Italy (1989), Spain (1994), Austria (2000), France (2006), Switzerland (2012), the Netherlands (2017), Denmark (2020), and Japan (2021). In most states in Brazil, treatment with AAT is obtained through legal action, with the exception of the Federal District, which has a protocol and has provided treatment in a specialized outpatient clinic since 2010. More reference centers are necessary to promote specialized diagnosis and treatment for patients with rare pulmonary diseases. There is no longer any doubt that severe AAT deficiency with emphysema requires enzyme replacement. We may discuss whether a higher dose than that recommended today would be more effective or what would be the FEV1 cut-off for starting replacement, but it is no longer appropriate to watch the patient's accelerated decline of pulmonary function and not perform AAT replacement. It is high time for CONITEC (National Commission for Technology Incorporation in the Unified Health System) to reassess its previous position; anyone with AATD will certainly be very grateful.

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