Arch Bronconeumol. 2018;54(7):361–362

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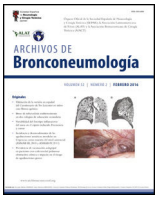

Editorial

Augmentation Therapy Nowadays: Con☆

Terapia de aumento en la actualidad: con

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Alpha-1 antitrypsin (A1AT) deficiency is a rare, incurable disease that is still underdiagnosed.[1,2] The risk of developing symptoms depends on A1AT concentrations and other factors such as smoking or pollution. Approximately 60% of A1AT deficiency patients who present a PiZZ phenotype develop lung disease, and 2%–3% of cases of chronic obstructive pulmonary disease (COPD) are thought have this deficiency.[3]

A relationship between the serum concentration of A1AT and the severity of emphysema (threshold of 11 μM/L) is assumed, and in theory, the administration of A1AT could prevent progression in patients with severe deficiencies.[4] Even so, the different reviews and studies have shown conflicting results.

Administration Schedules

A1AT product information recommends weekly administration, which impacts greatly on the use of this treatment. Other regimens have been evaluated, including 3-weekly and monthly schedules, but studies have shown that the pharmacokinetic properties of A1AT administered in infusions of 120 mg/kg/14 days and 180 mg/kg/21 days do not achieve the same concentrations as weekly dosing.[5] Strictly speaking, this implies that dosing should be weekly, but this complicates treatment for a large number of potential patients, taking into account that it must be administered for life. The possibility of increasing the dose per kg and altering the frequency of administration is still being debated.

Efficacy Variables

Initially, the efficacy parameter evaluated was reduction in forced expiratory volume in 1 s (FEV1). Results were inconclusive and unsupported by evidence from randomized studies. The main reason for this lack of quality studies is the need to include large numbers of patients in order to detect changes in this variable – a difficult task in this disease.

In the first randomized study, Dirksen et al.[6] assigned 56 patients with A1AT deficiency (Pi*ZZ) and FEV1 between 30% and 80% to receive A1AT 250 mg/kg or placebo for 3 years. The objective was to compare the rate of FEV1 reduction, but no significant differences were found between the groups. The mean annual rate of reduction in the placebo group was 25.2±22 ml vs 26.5±15.1 ml (P=0.96) in the treatment group, while no differences were found in variables such as diffusing capacity of the lung for carbon monoxide (DLCO). An analysis of patients included in a Spanish registry[7] revealed no differences in FEV1 progress between those who received or did not receive treatment, a result that the authors admitted was unexpected. This, and other studies with similar results, have led to a situation in which no single variable is currently used as a valid parameter.

Lung Density

The failure to prove FEV1 as a valid efficacy parameter prompted a search for other variables. In the above-mentioned study,[6] lung density measured by computed tomography (CT) was evaluated, revealing a non-significant trend (P=0.07) (2.6±0.41 g/l/year in the placebo group vs 1.5±0.41 g/l/year in the treatment group).

The same authors presented data from the EXAcerbations and CT scan as Lung Endpoints (EXACTLE) study,[8] a pilot project designed to assess the effect of treatment on loss of lung density measured by CT and on the number of exacerbations. Seventy-seven patients were randomly assigned to weekly infusions of treatment or placebo for 2.5 years. There were significant trends in lung density in favor of the treatment group (the mean slope of change in 15th percentile lung density (PD15) was 0.857 [−0.065 to 1.778]; P=0.07). Again no differences were detected in loss of lung function as measured by FEV1, DLCO, and exacerbation rates between groups. A subsequent analysis of these data confirmed that PD15 is the most sensitive index of the progression of emphysema.[9] A comparison of various densitometry indexes indicated that the result was affected by the inspiratory volume at which the measurement (PD15) was obtained. The data from these 2 studies were pooled and reanalyzed,[10] and the mean average change from baseline in lung density was found to be −4.082 g/l for A1AT, and −6.379 g/l

☆ Please cite this article as: Gáldiz Iturri J. Terapia de aumento en la actualidad: con. Arch Bronconeumol. 2018;54:361–362.

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for placebo, with a significant difference in favor in the treatment group.

Between 2006 and 2010, 180 patients with A1AT deficiency were randomized to receive replacement therapy (60 mg/kg) or placebo for 2 years in the RAPID-RCT study.[11] The annual rate of lung density loss at TLC alone was significantly less in patients in the treatment group (n=180; −1.45 g/l/year vs −2.19 g/l/year; P=0.017), but the same was not true of loss at FRC alone, while the annual rate of lung density loss at TLC and FRC combined did not differ between groups. This benefit was confirmed in the RAPID-OLE (open-label extension) study in which all patients received α1 proteinase inhibitor (A1PI). A similar study, the SPARTA trial, is currently ongoing.[12]

Mortality

Few research groups have investigated the impact of replacement therapy on mortality. A patient registry study[13] suggested that patients with FEV1 values <50% who received replacement therapy had greater survival than patients who did not. This study was not prospectively controlled to determine if the treatment was administered correctly, and uncontrolled factors between the treated and untreated groups may have confounded the findings.

Exacerbations

Neither of the studies mentioned above[6,8] have shown any impact on exacerbation, and some commonly cited publications raise methodological concerns.[14]

Two Cochrane reviews, one recently completed,[15] conclude that there is insufficient evidence to recommend replacement therapy. In summary, the effectiveness of replacement therapy has generated controversy since it was first marketed. It is costly, inconvenient for the patient (weekly, intravenous, life-long), and the variables initially used for evaluation (FEV1, exacerbations) have been proven invalid. In recent years, CT (PD15) has emerged as a useful tool for determining effectiveness, and results, which appear promising, remain to be confirmed in ongoing studies (SPARTA). Even so, we must not ignore the fact that to measure this parameter, certain technology (CT, software) is required that is unavailable in most hospitals.

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