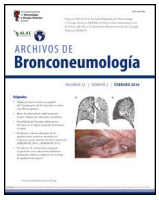
Arch Bronconeumol. 2018;54(7):363–364

Sociedad Española de Neumología y Cirugía Torácica SEPAR

ARCHIVOS DE Bronconeumología

www.archbronconeumol.org



Editorial

Augmentation Therapy for Emphysema due to Alpha-1 Antitrypsin Deficiency: Pro☆

Tratamiento aumentativo para el enfisema por déficit de alfa-1 antitripsina: Pro

Miriam Barrecheguren,[a] Marc Miravitlles[a,b,*]

[a] Servicio de Neumología, Hospital Universitari Vall d'Hebron, Barcelona, Spain
[b] CIBER de Enfermedades Respiratorias (CIBERES), Spain

Alpha-1 antitrypsin deficiency (AATD) is a hereditary disease characterized by low plasma levels of alpha-1 antitrypsin (AAT) and an increased risk of developing liver disease and pulmonary emphysema. AAT protects the lung tissue from destruction by elastase released by the neutrophils, so individuals with serum AAT concentrations below 0.50 g/l have a high risk of developing emphysema, particularly if they are smokers.

The only specific treatment available to date has been intravenous infusion of purified AAT derived from donor plasma. The aim of this therapy is restore AAT to normal levels, in order to inhibit the destructive action of proteases and thus prevent or decelerate the development of emphysema.[1]

This augmentation therapy has been shown to be effective, both biochemically and clinically. Biochemical efficacy is demonstrated by protective levels of AAT being maintained in blood and lung tissue,[2] and by the inhibition of elastase in the lung.[3] Moreover, this in vivo anti-elastase activity is confirmed by a reduction in urinary levels of desmosine and isodesmosine, indirect markers of elastin degradation in the lung and, thus, markers of reduced lung tissue destruction.[4] Clinical evidence of this phenomenon is demonstrated by a change in the natural history of the disease, as observed in the 3 clinical trials conducted to date.[5–7] Initially, 2 trials with small patient numbers[5] showed a reduction in lung density loss measured by computed tomography (CT) in patients receiving replacement therapy compared to placebo. Although the differences in both studies were at the limit of statistical significance due to the small sample size, a combined analysis found that replacement treatment was statistically highly superior.[5]

More recently, the RAPID study confirmed the efficacy of replacement therapy in preserving the pulmonary parenchyma.[6] This study, the largest conducted to date, included 180 patients with AATD and FEV1 35%–70%, randomized to receive replacement therapy or placebo for 2 years. Results showed that augmentation treatment delayed lung density loss. Moreover, in a 2-year open-label extension of the same study in which all patients received active treatment,[7] lung density loss decelerated significantly and to the same extent in patients who had previously received placebo (late treatment starters) and treatment (early treatment starters). However, lung density lost by the late starters during the first phase of the study was not recovered. This reduction in lung tissue loss has been also extrapolated to improved survival, with an estimated gain of 5.6 life years.[8] These data are consistent with results obtained from the American registry, which reported a significant reduction in mortality in severely ill patients who received treatment.[9] This increase in survival has been used to calculate the cost-effectiveness of augmentation therapy.[10] Using an estimated gain of between 7.4 and 10.6 years life years with augmentation treatment according to sex and smoking habit, the cost per year of life gained is between $59 234 and $248 361. While this may appear high at first glance, the cost/effectiveness ratio is similar to other widely used treatments, such as simvastatin for the prevention of ischemic heart disease at $195 000 per year of life gained.[10]

Why are questions still being raised about augmentation therapy?[11] Mainly because we are trying to evaluate its clinical efficacy using the same criteria applied to drug treatment for chronic obstructive pulmonary disease (COPD). If we base our conclusions on rate of decline of FEV1as the primary outcome of treatment efficacy, a great many patients will be needed to achieve sufficient statistical power.[12] For example, the primary outcome of the UPLIFT study was to evaluate the rate of decline of FEV1, and for that 6000 patients were required.[13] Obviously, this sample size is impossible to achieve with a rare disease like AATD. For the same reason, it is equally unfeasible to conduct a study powered to analyze mortality.[12]

Another argument against this therapy is its ineffectiveness against other COPD variables, such as exacerbations. Although AAT can inhibit the growth of certain bacteria,[14] its antiprotease mechanism does not suggest that it could be beneficial in the prevention of exacerbations. Moreover, a much greater number of patients than those included in the AAT studies would be required to design a study evaluating exacerbations.

Augmentation therapy has also failed to show benefits in patient-reported outcomes, such as dyspnea or physical activity,

☆ Please cite this article as: Barrecheguren M, Miravitlles M. Tratamiento aumentativo para el enfisema por déficit de alfa-1 antitripsina: Pro. Arch Bronconeumol. 2018;54:363–364.

* Corresponding author.
E-mail address: mmiravitlles@vhebron.net (M. Miravitlles).

but this should not be surprising given that AAT replacement is not a symptomatic treatment. In this respect, emphysema could be compared to osteoporosis, another disease caused by tissue destruction, in which treatment efficacy is determined mainly by densitometry and not by clinical parameters. AAT treatment efficacy should also be measured by lung densitometry, which is also the best predictor of mortality.[1]

More important evidence in favor of the efficacy of this treatment derives from a post hoc analysis of the RAPID study, which showed that the magnitude of lung tissue loss is inversely related with AAT levels achieved during augmentation therapy.[6] These data on the dose/response effect of the treatment reaffirm its efficacy, and have prompted the design of clinical trials using higher doses of AAT.[15]

In conclusion, augmentation therapy has proven its efficacy in reducing loss of lung density and, as such, the progression of emphysema. Clinical trials available to date have shown consistent results and provide sufficient evidence to support the use of this treatment in AATD patients with emphysema. The lack of evidence of its impact on clinical variables such as exacerbations or symptoms must not be used as an argument against its use, since this is an etiological approach rather than a symptomatic treatment, and accordingly, cannot be expected to affect those variables. For this reason, national and international guidelines[1,16] recommend the use of augmentation therapy in AATD patients with emphysema who meet the established criteria.

Conflict of Interests

Miriam Barrecheguren has received fees for speaking engagements from Grifols and Marc Miravitlles has received fees for speaking engagements from Grifols and CSL Behring and for consultancy services from Grifols.

References

1. Miravitlles M, Dirksen A, Ferrarotti I, Koblizek V, Lange P, Mahadeva R, et al. European Respiratory Society statement: diagnosis and treatment of pulmonary disease in α1-antitrypsin deficiency. Eur Respir J. 2017;50:1700610.
2. Wewers MD, Casolaro MA, Sellers SE, Swayze SC, McPhaul KM, Wittes JT, et al. Replacement therapy for alpha 1-antitrypsin deficiency associated with emphysema. N Engl J Med. 1987;316:1055–62.
3. Stockley RA, Bayley DL, Unsal I, Dowson LJ. The effect of augmentation therapy on bronchial inflammation in α1-antitrypsin deficiency. Am J Respir Crit Care Med. 2002;165:1494–8.
4. Ma S, Lin YY, He J, Rouhani FN, Brantly M, Turino GM. Alpha-1 antitrypsin augmentation therapy and biomarkers of elastin degradation. COPD. 2013;10:1–9.
5. Stockley RA, Parr DG, Piitulainen E, Stolk J, Stoel BC, Dirksen A. Therapeutic efficacy of alpha-1 antitrypsin augmentation therapy on the loss of lung tissue: an integrated analysis of 2 randomized clinical trials using computed tomography. Respir Res. 2010;11:136.
6. Chapman KR, Burdon JG, Piitulainen E, Sandhaus RA, Seersholm N, Stocks JM, et al. Intravenous augmentation treatment and lung density in severe alpha-1 antitrypsin deficiency (RAPID): a randomized, double-blind, placebo-controlled trial. Lancet. 2015;386:360–8.
7. McElvaney NG, Burdon J, Holmes M, Glanville A, Wark PA, Thompson PJ, et al. Long-term efficacy and safety of alpha-1 proteinase inhibitor treatment for emphysema caused by severe alpha-1 antitrypsin deficiency: an open label extension trial (RAPID-OLE). Lancet Respir Med. 2017;5:51–60.
8. Rahaghi FF, Miravitlles M. Long-term clinical outcomes following treatment with alpha 1-proteinase inhibitor for COPD associated with alpha-1 antitrypsin deficiency: a look at the evidence. Respir Res. 2017;18:105.
9. The Alpha-1 antitrypsin deficiency registry study group. Survival and FEV1 decline in individuals with severe deficiency of alpha-1 antitrypsin. Am J Respir Crit Care Med. 1998;158:49–59.
10. Sclar DA, Evans MA, Robison LM, Skaer TL. Alpha-1 proteinase inhibitor (human) in the treatment of hereditary emphysema secondary to alpha-1 antitrypsin deficiency, number and costs of years of life gained. Clin Drug Invest. 2012;32:353–60.
11. Gøtzsche PC, Johansen HK. Intravenous alpha-1 antitrypsin augmentation therapy for treating patients with alpha-1 antitrypsin deficiency and lung disease (Review). Cochrane Database Syst Rev. 2016;9:CD007851.
12. Schuchter MD, Stoller JK, Barker AF, Buist AS, Crystal RG, Donohue JF, et al. Feasibility of a clinical trial of augmentation therapy for alpha-1 antitrypsin deficiency. Am J Respir Crit Care Med. 2000;161:796–801.
13. Tashkin DP, Celli B, Senn S, Burkhart D, Kesten S, Menjoge S, et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. N Engl J Med. 2008;359:1543–54.
14. Hadzic R, Nita I, Tassidis H, Riesbeck K, Gjorloff Wingren A, Janciauskiene S. Alpha-1 antitrypsin inhibits *Moraxella catarrhalis* MID protein-induced tonsillar B cell proliferation and IL-6 release. Immunol Lett. 2006;102:141–7.
15. Sorrells S, Camprubi S, Griffin R, Chen J, Ayguasanosa J. SPARTA clinical trial design: exploring the efficacy and safety of two dose regimens of alpha1-proteinase inhibitor augmentation therapy in alpha1-antitrypsin deficiency. Respir Med. 2015;109:490–9.
16. Casas F, Blanco I, Martínez MT, Bustamante A, Miravitlles M, Cadenas S, et al. Indications for active case searches and intravenous alpha-1 antitrypsin treatment for patients with alpha-1 antitrypsin deficiency chronic obstructive pulmonary disease: an update. Arch Bronconeumol. 2015;51:185–92.