Arch Bronconeumol. 2018;54(9):451–452

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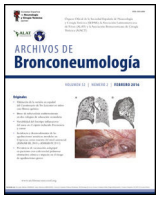

Editorial

# Are There Differences Between the Available Treatments for Emphysema Associated With Alpha-1 Antitrypsin Deficiency?☆

# ¿Existen diferencias entre los tratamientos disponibles para el enfisema pulmonar por déficit de alfa-1 antitripsina?

Cristina Esquinas, Marc Miravitlles*

*Servicio de Neumología, Hospital Universitari Vall d'Hebron, CIBER de Enfermedades Respiratorias (CIBERES), Barcelona, Spain*

The only specific treatment for emphysema associated with alpha-1 antitrypsin deficiency (AATD) is intravenous infusion of purified AAT from pooled human plasma. This product was developed in the United States[1] and approved by the U.S. Food and Drug Administration in 1987. The therapeutic goal is to raise and maintain AAT levels in plasma and in the pulmonary interstitium to prevent destruction of lung tissue and to stop the progression of emphysema.[1]

In Spain, replacement therapy was introduced at the end of the 1980s,[2] and 155 patients are currently receiving treatment, according to the Spanish Registry of Patients with Alpha-1 Antitrypsin Deficiency.[3] Several AAT preparations derived from human plasma are available for intravenous administration in Europe, but in this editorial we will focus on the comparison of products available in Spain: Prolastin® (Grifols Deutchsland GmbH, Germany) and Respreeza® (CSL Behring GmbH, Germany). Both are indicated for augmentation treatment in patients with severe AATD (PiZZ, PiZ null, Pi null null, and PiSZ genotypes) and evidence of pulmonary emphysema.[4] The recommended dose is 60 mg/kg/week administered at an infusion rate of 0.08 ml/kg/min,[5,6] although pharmacokinetic studies indicate that doses of 120 mg/kg/15 days can also achieve protective plasma concentrations for most of the time between administrations,[7] so this regimen is used in most cases, given its greater convenience for the patient.[3]

Prolastin® was the first treatment to be approved and is the most widely prescribed augmentation treatment worldwide; safety and tolerability have been established on the basis of records from 3 million infusions, with no episodes of viral transmission over a period of use of more than 25 years. Respreeza® was approved in 2016 by the European Medicines Agency, providing another option for AADT patients. Its use in the United States was approved by the Food and Drug Administration in 2003 (Zemaira® in the US) on the basis of its equivalent biochemical efficacy compared to Prolastin®.[8] In contrast, approval in Europe was delayed until clinical efficacy in the prevention of progression of emphysema was demonstrated.[9]

Both Prolastin® and Respreeza® are distributed in 1 g vials that are reconstituted in 40 ml of water for injection, in the case of Prolastin®, and in 20 ml in the case of Respreeza®. At the recommended infusion rate, an adult weighing 75 kg will complete the infusion of a weekly dose in 30 min for Prolastin®, and in 15 min for Respreeza®, and twice as long for the 2-weekly dosing.[5,6] Other differences between the products include the purity or proportion of AAT among all the plasma proteins found in the product. In the case of Respreeza®, purity is 97.4%, and for Prolastin®, it is 76.9%. Specific activity is also slightly different, at 86% for Respreeza® (0.862 mg of active AAT for each mg of protein), and 64% for Prolastin®.[10] It is interesting to note that there is no evidence of any correlation between purity, tolerability, and clinical efficacy, and that approval for the clinical use of Respreeza® was based on its proven equivalence with Prolastin®.[8]

With regard to clinical efficacy, 2 randomized, placebo-controlled clinical trials found that Prolastin® consistently reduced the decline in lung density measured by computed tomography. When analyzed together, a clear statistical significance was found in favor of active treatment.[11] Later, a similar clinical trial performed with Respreeza®, but with a larger sample size, showed a similar effect on the progression of emphysema.[9] Studies performed with Prolastin® showed a mean difference of 1.14 g/l/year in lung density decline, and the study with Respreeza® found a mean difference of 0.74 g/l/year.[9,11] It is difficult to compare the magnitude of these differences since the studies were performed at different times with different COPD treatment regimens.

There are some interesting differences in the indications listed in the Summary of Product Characteristics for both products. Prolastin® is indicated in patients with severe AATD within moderate limits of airway obstruction (FEV1 35%–60%) and a diagnosis of emphysema.[5] On the other hand, no lung function range is established for Respreeza®, while the possibility that the patient or the caregiver may personally administer the drug after receiving

☆ Please cite this article as: Esquinas C, Miravitlles M. ¿Existen diferencias entre los tratamientos disponibles para el enfisema pulmonar por déficit de alfa-1 antitripsina? Arch Bronconeumol. 2018;54:451–452.

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

the initial doses in the hospital is mentioned. It is important to emphasize that the product must be indicated by an expert in the treatment of AATD.[6] The varying clinical expression of AATD, the possibility of personalized treatment,[12] and the difficulty in acquiring the necessary experience in management due to the rarity of the disease, have prompted both the European Commission and the European Respiratory Society to recommend that treatment is indicated and monitored in reference centers.[13]

Finally, although Prolastin® and Respreeza® have very similar characteristics, blood products must not be switched, as this would lead to a loss of traceability in the event of the appearance of adverse effects or communicable diseases. Moreover, a pharmacist cannot change the medical prescription of a blood product, as stated clearly in article 86.4 of Law 29/2006 on guarantees and rational use of medicines and medical devices of the Ministry of Health, Social Services, and Equality.[14]

Until new therapeutic options appear, augmentation therapy with AAT is the only specific treatment for patients with congenital emphysema. The 2 products available in Spain have demonstrated effectiveness in slowing the progression of emphysema,[15] so this treatment must be made available to patients who meet internationally accepted criteria, and must be monitored and supervised in reference centers.[13]

## Conflict of interests

Cristina Esquinas collaborates in the management of the Spanish Registry of Patients with Alpha-1 Antitrypsin Deficiency, funded by Grifols. Marc Miravitlles has received fees for speaking engagements from Grifols and CSL Behring and for consultancy services from Grifols.

## References

1. Wewers MD, Casolaro MA, Sellers SE, Swayze SC, McPhaul KM, Wittes JT, et al. Replacement therapy for alpha 1-antitrypsin deficiency associated with emphysema. New Engl J Med. 1987;316:1055–62.
2. Vidal R, Miravitlles M, de Gracia X, Gallego B, Morell F. Tratamiento sustitutivo del enfisema por déficit de alfa-1-antitripsina. Med Clin (Barc). 1991;96:180–2.
3. Lara B, Blanco I, Martínez MT, Rodríguez E, Bustamante A, Casas F, et al. Spanish registry of patients with alpha-1 antitrypsin deficiency: database evaluation and population analysis. Arch Bronconeumol. 2017;53:13–8.
4. 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.
5. Prolastina. Summary of Product Characteristics (SPC). Available from: http://grifols.com/documents/10192/27754341/ft-prolastin-es-en/786cce6a-effb-41b6-867f-59d7a34ca086 [accessed 17 December].
6. Respreeza. Summary of Product Characteristics (SPC). Available from: https://ec.europa.eu/health/documents/community-register/2015/20150820132594/dec_132594_es.pdf [accessed 17 December].
7. Soy D, de la Roza C, Lara B, Esquinas C, Torres A, Miravitlles M. Alpha-1-antitrypsin deficiency: optimal therapeutic regimen based on population pharmacokinetics. Thorax. 2006;61:1059–64.
8. Stocks JM, Brantly M, Pollock D, Barker A, Kueppers F, Strange C, et al. Multicenter study: the biochemical efficacy, safety and tolerability of a new alpha1-proteinase inhibitor, Zemaira. COPD. 2006;3:17–23.
9. Chapman KR, Burdon JG, Piitulainen E, Sandhaus RA, Seersholm N, Stocks JM, et al. Intravenous augmentation treatment and lung density in severe α1 antitrypsin deficiency (RAPID): a randomised, double-blind, placebo-controlled trial. Lancet. 2015;386:360–8.
10. Boerema DJ, An B, Gandhi RP, Papineau R, Regnier E, Wilder A, et al. Biochemical comparison of four commercially available human $\alpha_1$-proteinase inhibitors for treatment of $\alpha_1$-antitrypsin deficiency. Biologicals. 2017;50:63–72.
11. 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 randomised clinical trials using computed tomography densitometry. Respir Res. 2010;11:136.
12. Stockley RA, Miravitlles M, Vogelmeier C. Augmentation therapy for alpha-1 antitrypsin deficiency: towards a personalised approach. Orphanet J Rare Dis. 2013;8:149.
13. 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 alpha-1 antitrypsin deficiency. Eur Respir J. 2017;50:1700610.
14. Orden SCO/2874/2007, de 28 de septiembre, por la que se establecen los medicamentos que constituyen excepción a la posible sustitución por el farmacéutico con arreglo al artículo 86.4 de la Ley 29/2006, de 26 de julio, de garantías y uso racional de los medicamentos y productos sanitarios. Available from: https://www.boe.es/buscar/doc.php?id=BOE-A-2007-17420 [accessed 17 December].
15. 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.