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Augmentation Therapy for Alpha-1 Antitrypsin Deficiency—Not Enough Evidence to Support its Use Yet!

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Letter to the Editor

Augmentation Therapy for Alpha-1 Antitrypsin Deficiency – not enough evidence to support its use yet!

To the Editor,

In their meta-analysis, Chapman et al [1] suggest that augmentation therapy for alpha$_1$-antitrypsin (AAT) deficiency can slow lung function decline and will likely benefit those with moderate airway obstruction. We believe that there is only limited evidence to support augmentation therapy on current data and that this meta-analysis has several inconsistencies or flaws.

As acknowledged by the authors, the analysis was limited by the small number of studies included and with almost 60% of the 1509 patients taken from the NHLBI Registry, a non-randomised retrospective study. The only randomised control trial was a small study by Dirksen et al. [2] which, on its own only, showed a favourable trend in improving CT densitometry but no benefit on FEV1. Also, no analysis of an eventual publication bias has been reported, either.

Importantly, we feel the study by Wencker et al [3] is inappropriate in its inclusion in this meta-analysis due to weaknesses in the methodology. Patients in this study were used as their own controls. The results in this case may actually represent a patho-physiological pattern of decline in lung function that occurs in COPD and AAT rather than a consequence of therapy, therefore, these need to have been adjusted for such eventual physiological decline. Additionally, an average of two FEV1 measurements before and after augmentation therapy is insufficient to demonstrate or refute a progressive decline in lung function (usually, a trend and its slope are defined by at least 3 points in time).

Other confounding factors that were not analysed but may impact on lung function were the varying lengths of studies and time periods during which they were completed. Studies analysed were published over a 9-year period (from 1997 to 2005 inclusive). Treatment modalities such as Tiotropium, which have been shown to have significant impact on lung function preservation [4] became available and were adopted into widespread clinical use thus, potentially, may have altered the results substantially.

Finally, we feel that representation of the results for lung volumes as a percentage is misleading. While the authors have demonstrated a trend to support augmentation therapy, we feel that the volume of approximately 18 ml per year seems negligible. After 11 years treatment only 200 ml more of lung volume would be preserved. The questions that remain unanswered are whether this has significant clinical impact for the patient and if it is cost-effective? Augmentation therapy for alpha$_1$-antitrypsin is very expensive, costing up to $150,000 [5] with annual costs averaging $40,000 per individual patient.[6] A larger randomised control trial with enough power to adequately assess efficacy and effectiveness is needed. Bearing this in mind, we feel this meta-analysis provides insufficient evidence to support augmentation therapy at present.

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