Augmentation therapy for alpha1 antitrypsin deficiency: a meta-analysis

CRD summary
The authors concluded that augmentation therapy slowed lung function decline in patients with alpha1-antitrypsin deficiency, with patients with moderate obstruction (forced expiratory volume in one second of 30 to 65%) most likely to benefit. Much of the review was well-conducted, but reliance upon predominantly non-randomised studies of unknown quality made it difficult to confirm the reliability of these conclusions.

Authors' objectives
To test the hypothesis that augmentation therapy with exogenous alpha1-antitrypsin, in patients with alpha1-AT deficiency, slows the decline in lung function, as measured by forced expiratory volume in one second (FEV1).

Searching
MEDLINE, EMBASE, the Cochrane Library and internet conference report sites were searched for articles in any language. Search terms (but not search dates) were reported. Handsearching of selected journals was also undertaken. Investigators and manufacturers were contacted for information on relevant studies. Reference lists of retrieved articles were also scanned.

Study selection
Parallel-group and single cohort pre-test/post-test studies comparing augmentation therapy versus a control therapy in patients with alpha1-antitrypsin deficiency were eligible for inclusion. Studies had to provide forced expiratory volume in one second (FEV1) data over at least one-year. Uncontrolled studies and case reports were excluded.

The included studies compared augmentation therapy with a control or prior to augmentation therapy in patients with alpha1-antitrypsin deficiency. All reported FEV1 values over at least three years follow-up. The majority of included patients were ex-smokers.

Two reviewers performed the study selection and differences in opinion were resolved through discussion.

Assessment of study quality
Study quality was assessed according to a number of criteria: prospective versus retrospective data collection; study size; and (in the case of randomised trials) blinding and allocation concealment.

The authors did not state how many reviewers performed the quality assessment.

Data extraction
Data were extracted of FEV1 rates at baseline and FEV1 percent predicted. Investigators were contacted for missing data were necessary.

Two reviewers performed the data extraction and differences in opinion were resolved through discussion.

Methods of synthesis
Random effects meta-analysis was undertaken on the pooled differences in FEV1 slopes. For individual patient data, reported in one study, linear mixed modelling was employed. Heterogeneity was assessed. Publication bias was assessed using the Egger test. Sensitivity analysis was also undertaken.

Results of the review
Five studies were included (n=1,509 patients): one randomised controlled trial (n=56 patients); three parallel-group comparative studies (n=1,357 patients); and one pre-test/post-test study (n=96 patients). Data collection was at least
partially prospective in all five studies. The single RCT was double-blind, but the method of allocation concealment was unclear. Publication bias was not present in the analysis, but there was evidence of statistical heterogeneity (p=0.012) for the main analysis.

Overall, augmentation with alpha₁-antitrypsin was associated with a slower decline in the forced expiratory volume in one second (FEV₁) slope than control groups (slope difference 13.4mL/year, 95% CI 1.5 to 25.3; five studies).

Augmentation was most effective in patients with a baseline FEV₁ of 30 to 65% (slope difference 17.9mL/year, 95% CI 9.6 to 26.1; four studies).

In patients with a baseline FEV₁ of less than 30% (four studies) or greater than 65% (three studies), there was no statistically significant benefit of augmentation compared with control groups.

Sensitivity analysis indicated that the results were generally robust.

Authors' conclusions
Augmentation therapy slowed lung function decline in patients with alpha₁-antitrypsin deficiency. Patients with moderate obstruction (FEV₁ of 30 to 65%) were most likely to benefit.

CRD commentary
Inclusion criteria for the review were clearly defined and several relevant sources were searched. No language restrictions were imposed, which minimised language bias. Unpublished studies were sought and publication bias was assessed and was not found to be a problem. Study selection and data extraction were performed in duplicate, which minimised the potential for error and bias.

Study quality assessment was limited and was not based on a validated tool, which made it difficult to judge the quality of the evidence. Studies were combined using meta-analysis and study heterogeneity was explored, which was appropriate.

Much of the review was well conducted, but the dependence upon predominantly non-randomised studies of unknown quality means that the reliability of the conclusions is unclear.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that further studies of augmentation in patients with mild obstruction (FEV₁ less than 65%) or severe obstruction (FEV₁ more than 30%) are needed.

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