Augmentation therapy for severe α_1-antitrypsin deficiency: is the jury still out on a trial?

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As with the administration of insulin for diabetes mellitus, the rationale for administering purified α_1-antiprotease in severe α_1-antitrypsin (α_1AT) deficiency—a treatment dubbed "augmentation therapy"—is to provide the substance whose deficiency is deemed responsible for the pulmonary sequelae of α_1AT deficiency. Indeed, even as intravenous augmentation therapy has been advocated for severely deficient individuals with established airflow obstruction by some official societies (but not all),[1 2] and even as one commercial product has been licensed by the United States Federal Drug Administration with other intravenous and inhaled preparations currently under investigation, the efficacy of augmentation therapy continues to be actively debated. As with many controversies in medicine, this one centres on the nature and adequacy of available supportive evidence versus the gaps in current knowledge. In the wake of the recently published outcome data from the American National Heart, Lung, and Blood Institute (NHLBI) sponsored Registry of Patients with Severe Deficiency of α_1-Antitrypsin,[3] and a European comparison between rates of decline in forced expiratory volume in one second (FEV_1) in untreated Danish versus treated German subjects with α_1AT deficiency,[4] it is appropriate to examine the current state of evidence regarding augmentation therapy for severe α_1AT deficiency and to re-assess the evidence supporting this practice. This editorial takes an epistemological view of the evidence—how do we know what we know and is the evidence compelling? Also, in the context of current views, what are the implications of present knowledge on future studies of emerging treatments?

To consider current evidence about the efficacy of augmentation therapy, it is useful to recall a debate in medicine that consumed attention approximately 100 years ago—how to prove that an infectious agent was responsible for causing infection? Just as Dr Robert Koch proposed criteria that had to be satisfied before concluding infectivity[5]—rules now known as Koch's postulates—so it is useful to articulate the lines of evidence that must be satisfied in order to accept the efficacy of intravenous augmentation therapy for severe deficiency of α_1AT. Indeed, three such lines of evidence have been proposed[6]: (1) intravenous augmentation therapy must be able to raise serum and lung levels of α_1AT above the putative "protective threshold" values; (2) the functional anti-neutrophil elastase activity of the infused protein must be preserved in the serum and lung; and (3) augmentation therapy must be shown to have clinical efficacy to forestall the progression of emphysema in individuals at risk, and to do so safely.

Taken together, the first two of these criteria address the "biochemical efficacy" of intravenous augmentation therapy and are generally regarded to have been satisfied based on the following lines of evidence[6–9]:

1. Intravenous infusion of purified α_1-antiprotease once weekly (60 mg/kg) or once monthly (250 mg/kg)[8] has been shown to augment serum levels of α_1AT, such that nadir levels—that is, those immediately before the next infusion—generally remain above the putative "protective threshold" serum value of 11 μM. (Interestingly, biweekly infusions at a dose of 120 mg/kg appear not to maintain serum levels above 11 μM throughout the dosing interval[9].)
2. α_1AT is detectable in bronchoalveolar lavage fluid following weekly intravenous infusions of purified α_1-antiprotease,[6–8 10] indicating that the intravenously administered protein has traversed the lung interstitium; indeed, the levels of both α_1AT and of neutrophil elastase inhibitory activity in the epithelial lining fluid also exceed suggested protective levels.
3. In two individuals with severe α_1AT deficiency intravenous infusion of purified pooled human α_1-antiprotease (60 mg/kg once weekly) was associated with a significant decline in urinary desmosine levels, suggesting slowed elastolysis.[11]

Notwithstanding the persuasiveness of this evidence regarding "biochemical efficacy" and the conceptual appeal of raising levels of a substance whose deficiency is pathogenetic for the associated emphysema, the "clinical efficacy" of intravenous augmentation therapy—addressed by the third criterion above—is less certain because no randomised controlled trial of augmentation therapy has been performed. Until the recent availability of observational cohort studies comparing individuals treated and those not treated with augmentation therapy,[3 4] there were two lines of evidence to support the clinical efficacy. Firstly, despite obvious study limitations such as the lack of comparative groups, the brevity of the follow up period (≤18 months), and the small number of patients examined (≤28 patients per study), early feasibility studies of intravenous augmentation therapy showed no decline in lung function (FEV_1 and transfer factor) or progression of chest radiographic features of emphysema in recipients over the period of follow up.[6–8] Secondly, a preliminary report regarding post hoc analysis of FEV_1 slopes in German recipients of augmentation therapy showed that those patients who experienced fewer bronchitic episodes while receiving augmentation therapy had a lower rate of decline of FEV_1 than those whose frequency of bronchitic episodes was unchanged.[12] Both lines of evidence fall far short of proving clinical efficacy.

With the recent publication of results from two observational studies (the German-Danish study published in 1997[4] and the recently published NHLBI Registry study[3]), additional evidence supporting the clinical efficacy of intravenous augmentation therapy has become available. Results from both studies indicate that the rate of decline of FEV_1 in individuals with moderately severe COPD (FEV_1 31–49% predicted and 31–65% predicted, respectively) was significantly lower among those treated with augmentation therapy than among those not treated. Still, it is reasonable to question whether these results establish the clinical efficacy of augmentation therapy or whether methodological reservations about these observational studies warrant continued uncertainty.

In the German-Danish study reported by Seersholm *et al*,[4] serial FEV_1 measurements were made in two groups of patients with severe α_1AT deficiency—a German cohort of 198 eligible ex-smokers (culled from a surveillance group of 443 patients) who received weekly infusions of purified pooled human antiprotease (Prolastin HS at 60 mg/kg,

Bayer, Leverkusen, Germany) and a Danish cohort of 97 ex-smokers who were not given augmentation therapy (the "untreated" group). Comparison of the rate of decline of FEV_1 showed that, for the groups overall, the mean rate was lower in the treated than the untreated patients (–53 ml/year versus –75 ml/year, p = 0.02). Post hoc subset analysis showed that this lower rate of decline in treated patients was due to the significantly lower rate of FEV_1 decline among treated patients with initial FEV_1 values between 31% and 65% predicted (–62 ml/year versus –83 ml/year, p = 0.04), but that no difference in FEV_1 slopes was evident in patients with baseline FEV_1 values either below 31% predicted or above 65% predicted. As pointed out by the investigators themselves and by Hutchison and Hughes in an accompanying editorial,[13] caution is required in interpreting the results because the study used an observational cohort design rather than using randomised allocation of augmentation therapy. Thus, differences in the outcome measure—that is, rate of change of FEV_1—cannot be confidently ascribed to the augmentation therapy but may reflect either baseline or other treatment differences between the compared groups. As an example of known baseline imbalances in the study, the German cohort had a higher percentage of men and a lower initial FEV_1 % predicted than the Danish group. Lack of randomisation invites the possibility of other important but undetected baseline differences. Also, it is unclear from the published report whether the FEV_1 measurements in the Danish cohort were post-bronchodilator values as in the German group, and whether other "co-therapies" for COPD such as inhaled bronchodilators were similarly administered to the two groups. Hutchison and Hughes[13] cite an earlier estimate of the mean FEV_1 slope of –59 ml/year that was based on 74 ex-smokers from the same Danish registry and point out that, had the earlier value been used for comparison with the mean FEV_1 slope in the German treated cohort (–53 ml/year), no significant difference would have been observed between the compared groups.

Most recently, results from the American NHLBI Registry for Patients with Severe Deficiency of α_1-Antitrypsin have become available[3] and also show that use of intravenous augmentation therapy is associated with benefits. Specifically, multivariate analyses showed that patients receiving augmentation therapy experienced a lower mortality risk (risk ratio 0.64, p = 0.02) and that the subset of patients receiving augmentation therapy with stage II COPD (FEV_1 35–49% predicted) experienced a slower rate of decline in FEV_1 (by 26.7 ml/year, p = 0.03) than untreated patients, although the rate of decline in FEV_1 for the entire group of patients treated with augmentation therapy did not differ significantly from that of untreated patients.

As amply pointed out by the authors of the study, methodological shortcomings of the Registry study must also be considered in interpreting these results. Firstly, the Registry cohort was not population based so the results may not be applicable generally to all patients with severe α_1AT deficiency. Secondly, with regard to the "internal validity" of the study,[14] despite careful statistical modelling to address baseline differences between those treated with augmentation therapy and those not treated, the possibility that outcome differences relate to socioeconomic differences between the two groups could not be excluded. With these interpretative cautions in mind, the observed benefits of enhanced survival and a slower decline in FEV_1 in those patients with stage II COPD treated with augmentation therapy lend support to the clinical efficacy of augmentation therapy and extend the European data supporting the biological efficacy of intravenous augmentation therapy,[3] but do not establish its clinical efficacy.

Although the NHLBI Registry was conceived because a randomised clinical trial was initially deemed unfeasible,[15] the observation that values for the variance around FEV_1 slope estimates from the NHLBI Registry are lower than those used in earlier power calculations[15 16] suggests that such a trial now seems more feasible by virtue of its requiring fewer patients in each study arm than was originally projected. Two significant impediments to conducting a randomised clinical trial of intravenous augmentation therapy still remain, however, at least in the USA. Firstly, the expense of such a trial would be daunting, even if as few as 100 subjects were treated for as briefly as three years. Specifically, based on a drug cost of $30 000 per subject per year, the cost of intravenous augmentation therapy alone in such a trial would total $3 million, even before considering the additional costs of clinical testing, data analysis, and administration of the trial. It seems likely that such costs would dissuade prospective corporate sponsors and even government from organising such a trial. A second no less formidable impediment is that, despite the steadfast commitment by patients with α_1AT deficiency to support research, it seems unlikely that patients would accept allocation to a placebo arm in the context of available evidence, however imperfect, suggesting that intravenous augmentation therapy has clinical efficacy. Such understandable reluctance by patients may be the immutable legacy of the earlier decision to forego a randomised controlled clinical trial when the first commercial preparation of pooled human α_1-antiprotease was proposed for intravenous infusion.

Accepting that a placebo controlled randomised clinical trial of intravenous augmentation therapy seems regrettably unlikely in the USA, what are the prospects for conducting definitive randomised placebo controlled trials of future alternative therapies? In the specific case of inhaled augmentation therapy, because available evidence regarding both biochemical and clinical efficacy is sparse, the prospects of conducting a randomised controlled trial seem brighter. In particular, a "double dummy" randomised trial design has appeal because it would allow comparison of inhaled with intravenous augmentation therapy. Specifically, participants in one arm would receive active inhaled α_1-antiprotease and placebo infusions, while subjects in the other arm would receive active α_1-antiprotease intravenously but a placebo inhaled agent. Although it is, admittedly, an ambitious goal, perhaps the impetus to rigorously evaluate the efficacy of a new but sparsely studied agent would motivate inclusion of a third study arm in which participants would receive a placebo intravenously and also by inhalation. Certainly, as with earlier considerations in designing a randomised trial of intravenous augmentation therapy, this design proposal must be subjected to careful review regarding statistical and practical feasibility. Indeed, in the absence of available estimates of the effect of inhaled augmentation therapy, it is likely that the best available power calculations for a future trial of inhaled therapy will be based on calculations that are expected from the NHLBI Registry.

However ambitious the recruitment and study requirements for future randomised trials appear, several new understandings about α_1AT deficiency, about the community of affected individuals, and about their deep interest in optimal treatment certainly enhance the prospects for a future randomised trial. Firstly, in North America the NHLBI Registry has demonstrated the feasibility of recruiting a large cohort of severely deficient individuals. Indeed, the recruitment goal of 1000 was exceeded by the final Registry cohort of 1129 individuals. Furthermore, experience at the 37 participating clinical centres suggests that large numbers of newly diagnosed individuals with

severe deficiency continue to come to attention, even years after recruitment to the Registry closed in October 1992. Increased clinical recognition of α_1AT deficiency has also been encouraged by the activities of strong patient advocacy organisations such as the Alpha One Foundation and the Alpha 1 National Association, the availability of a national reference laboratory in Utah, and the outreach efforts of a newly formed research registry (the Alpha One Foundation Research Network) which has been organised and funded by the α_1AT patient community. Indeed, in fewer than its first six months of recruitment this new research network registry has already enrolled 521 subjects with α_1AT deficiency, reflecting enthusiasm by the patient community to support and encourage new research. Secondly, the fact that only 5–10% of severely deficient individuals in the USA are currently known supports the belief that these ongoing efforts to increase clinical recognition could identify far more individuals than are currently known. Indeed, assuming that currently revised power calculations for a randomised trial of intravenous augmentation therapy apply, it seems likely that enough new patients with α_1AT deficiency will be identified to satisfy the power requirements for a randomised trial of inhaled therapy. Thirdly, the greater efficiency of delivering inhaled α_1-antiprotease directly to the lung lowers the dose requirements and the projected drug costs of a trial of inhaled augmentation therapy. Finally, fervour by the patient and scientific communities—for example, the World Health Organisation[17] and the Canadian Thoracic Society[2]—to conduct definitive randomised trials to address the efficacy of new drugs should encourage at least a two arm double dummy (if not a three arm) placebo controlled randomised trial of inhaled augmentation therapy. Although there are formidable challenges to organising a future randomised trial, there is also currently an opportunity for a collaborative effort between government, a consortium of interested pharmaceutical companies, insurers, and the patient and scientific communities. Indeed, a precedent for such a novel collaboration between insurers, beneficiaries, a private foundation, and the academic community to organise a trial can be cited in the Overholt-Blue Cross/Blue Shield Emphysema Surgery Trial (OBEST), a multicentre randomised trial of lung volume reduction surgery that is currently underway in New England under the auspices of several insurance companies and the Overholt Foundation.

In the best tradition of clinical medicine, treatment decisions must be guided by the best available evidence. However deficient, the best current evidence certainly supports the clinical efficacy of augmentation therapy, at least in α_1AT deficient individuals with moderate airflow obstruction. At the same time, methodological shortcomings of the best available studies require that some uncertainty remains about the clinical efficacy of intravenous augmentation therapy. These methodological shortcomings and the resultant uncertainty vitiate the argument that a randomised controlled trial is ethically indefensible, especially when we remember that exogenous augmentation therapy may incur risk and concern. In the case of intravenous infusions, augmentation therapy has elicited concern about the risk of transmitting disease, and about the expense of both the drug and its administration. In the context that a randomised trial of intravenous augmentation therapy now seems statistically feasible, that new α_1AT deficient individuals continue to be recognised in large numbers, and that the α_1AT patient community is both organised and highly motivated to support rigorous studies, there are new opportunities to organise a randomised placebo controlled clinical trial of inhaled augmentation therapy. Remembering earlier editorial pleas for a randomised controlled trial to verify the efficacy of coronary artery revascularisation lest "the genie be allowed to escape from the bottle again",[18] we should find a way.

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