EDITORIAL

Revisiting α_1 -antitrypsin therapy in cystic fibrosis: can it still offer promise?

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The contribution of the neutrophil-derived serine protease neutrophil elastase (NE) to lung disease in cystic fibrosis (CF) is unquestioned and yet, despite promising preliminary studies in the last 20 yrs to investigate an effective therapy to negate the damaging effect of NE [1], this treatment has failed to take off for patients with CF. This is largely due to the scarcity of clinical trial data relating to this therapy. However, two recent publications [2, 3] signal a renewed interest in the application of treatment with inhaled α_1 -antitrypsin (AAT) as a panacea for the proteolytic damage occurring in CF lung disease.

NE is released by neutrophils either on the cell membrane during cell migration or into the extracellular space upon stimulation by immune complexes, or by necrotic or apoptotic cells [4]. AAT is one of the most important protease inhibitors involved in confining tissue proteolysis during an inflammatory response [5]. Secreted by the liver, increased AAT concentrations are stimulated by interleukin (IL)-6 and it acts rapidly in the peripheral tissue to inhibit serine proteases, such as NE, cathepsin G and proteinase 3. While it is believed that AAT secretion is not impaired in CF [6], there are an overwhelming number of activated neutrophils in the lungs, the product of which is an excessive release of NE and other proteases, which cannot be contained by physiological AAT levels.

In the current issue of the *European Respiratory Journal* GRIESE *et al.* [2] present findings on a prospective randomised study of AAT in CF. Griese *et al.* [2] set out to compare two different deposition patterns of inhaled AAT over a 4-week period to see which of the two provided the best clinical outcome. To achieve this they employed the new technology of individually programmed SMART CARDS, which were used to assign an inhalation pattern resulting in either bronchial or peripheral deposition. The primary variable of this study was a change in free NE activity, alongside AAT levels, percentage of polymorphonuclear cytokines in sputum, lung function parameters, exacerbations and adverse events. As there was no observed difference in any of the parameters relating to the site of deposition, the authors combined data from both study

arms to investigate the effect of inhaled AAT treatment. They found a significant decrease in each of the inflammatory parameters measured following treatment. Decreases in cytokines and cells were related to the decrease in free NE [2].

The limitation of this study, as recognised by the authors, was the lack of a placebo control, a result of the original study design, to compare two inhalation techniques. While the study by GRIESE *et al.* [2] will add to current knowledge, it is essential that new studies in this area incorporate proper placebo-controlled design in order for knowledge of this therapy to advance.

This study is the second study to show a significant reduction in elastase activity in subjects with CF following aerosol treatment of AAT [1, 2]. This trend was also supported (although it did not reach significance) in the only placebo-controlled trial of AAT reported to date by MARTIN *et al.* [3].

Studies looking at inhaled AAT have yet to find a significant effect on lung function. Since these studies have all been conducted in adults with established lung disease, lung function decline may have reached an irreversible point and reduction in NE activity may, at best, slow the progress, an effect best observed with a longer study period. Since all studies of inhaled AAT have also been of short duration (≤ 4 weeks), it is difficult to perceive a change in pulmonary function tests, driven by lowering inflammation, over this short period of time.

A constraint of each of the prior studies is that they have been conducted in adults with established lung disease where the confounding effect of sputum blockage may prevent the penetration of AAT into the smaller airways and periphery, resulting in the observed minimal effect. Then again, it may be that NE levels are so high in subjects tested to date that a much higher dose is necessary to effect a clinically significant change in NE levels. It may be that a reduction of NE back to zero is necessary to effectively delay proteolytic lung damage and fibrosis.

It is also possible that the minimal effect of AAT on secondary outcome variables is related to the fact that NE is only one component of the proteolytic barrage on the lung and AAT therapy may only negate one aspect of this, necessitating a second look at whether this treatment can be beneficial in isolation. Other products of the inflammatory response, such as matrix metalloproteases, and oxidants, such as myeloperoxidase (MPO), contribute to tissue damage in CF [7, 8] and are not effectively inhibited by AAT.

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It is encouraging that some of these fore-runner studies have found a common thread of enhanced host defence to bacteria [1–3], and reduced inflammation has been noted in all studies using a variety of different markers in each study (MPO, cell counts, cytokine expression and secretion). As NE is a potent stimulant of the neutrophil chemokine IL-8 [9], a decrease in this cytokine may be the first effect of reduced NE, suggesting that a longer course of treatment may yield more promising results in reducing inflammation. This is supported by the findings of GRIESE *et al.* [2], which showed a significant reduction in protein detected and mRNA expression of the pro-inflammatory cytokines IL-8, tumour necrosis factor- α and IL-1 β , along with a drop in the percentage of neutrophils present over the 4-week treatment period.

An important step forward in the area of prevention of lung disease in CF will no doubt be when anti-inflammatory and/or anti-proteolytic treatments can be applied at the time of lung disease initiation. The key to healthy adults with CF will be to keep their lungs healthy throughout childhood.

Is it possible that a return to undetectable NE may not be achievable in adults with established disease, but if applied to younger children with CF at the initiation of lung disease, this therapy could have a major impact on long-term outcomes. For example, bronchoalveolar lavage (BAL)-based studies of NE activity in young children show that it is not unusual for children with early lung disease to have undetectable or low levels of NE [10, 11] with median levels being 5–10 times lower [12] than those found in the sputum of adults reported in the study by GRIESE *et al.* [2]. Therefore, a reduction back to zero in children with early stage lung disease may well be achievable and sustainable with ongoing therapy. A thorough investigation of AAT therapy in young children would need to be conducted over longer periods of time to see an effect and issues around frequent sampling of the lower airways in this group is difficult as many children are not capable of expectoration. Consideration of other outcome variables will be an important issue in longitudinal studies to confirm that negating NE can significantly affect the cycle of inflammation and the clinical decline that ensues. If AAT therapy can be shown to reduce NE back to undetectable levels but does not have a significant clinical effect at that point, then one must conclude that NE is not the key component of the inflammatory cycle that it is currently thought to be.

There is no doubt now that lung disease begins in early childhood and there is a strong belief that this lung disease can and should be prevented or at least delayed for the best long-term clinical outcomes. Therefore, the real future of AAT therapy, if effective, lies in its application to young children at the beginning of the inflammatory process. Confirmation of efficacy would require a long-term multicentre study. One of the confounding issues associated with such a study is determining which outcome variable is appropriate as it is largely accepted that forced expiratory volume in one second (a gold standard for adults) is an insensitive marker of early structural lung dysfunction. Apart from assessment of BAL and sputum, a number of alternative methods for assessing lung function

and structure including high-resolution computer tomography, raised volume rapid thoracic compression, forced oscillation technique, multiple breath gas wash-out technique and measurement of the elastin breakdown product desmosines, are all candidates for outcome variables for such a clinical trial.

Studies being conducted both in Australia and the USA investigating a variety of these parameters will shed light on the most appropriate tools for use in clinical trials of the pre-school cystic fibrosis population in the near future. An important point to note about each of the studies of inhaled α_1 -antitrypsin was that no serious adverse events arose and safety outcomes were favourable [1–3]. This encourages future studies.

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