PostScript

LETTERS

High dose intravenous AAT and plasma neutrophil derived fibrinogen fragments

A recent review by Stoller and Aboussouan presented the current understanding of intravenous augmentation therapy for α_1-antitrypsin (AAT) deficiency.[1] Their criteria for demonstrating efficacy of this therapy did not include evidence of protection against lung tissue destruction. Such studies would show that sufficient levels of AAT are reached in the lungs to allow inhibition of neutrophil derived enzymes before they degrade elastin fibres to cause alveolar destruction—the hallmark of emphysema. To date, no such evidence has been presented. A study with the currently recommended augmentation regimen using assays of elastin degradation products failed to show any efficacy.[2] The authors argued that the duration of treatment was probably too short, but one may also argue that the dose was too low.

Ever since the introduction of AAT augmentation therapy, no clinical benefit has been demonstrated in a randomised clinical trial. However, the direct health care costs associated with AAT deficiency are high.[1] As no effect of this treatment on lung function has been proven, the question arises as to whether the currently recommended dose is high enough to achieve the desired biochemical and clinical effect.

We studied the effect of two different doses of intravenous AAT on neutrophil mediated proteolysis. Plasma levels of large fibrin(ogen) fragments formed by neutrophil elastase mediated degradation (PMN-FDP) were measured. These fragments are significantly higher in the plasma of subjects with AAT deficiency than in healthy controls, indicating an imbalance in the protease-antiprotease ratio in vivo at sites of inflammation where fibrin(ogen) is deposited.[3] Although not disease specific, fibrinogen is present at sites of inflammation and, as such, is relevant for patients with AAT deficiency who have increased inflammation in their lungs, even in the absence of a smoking habit.[4]

Twenty subjects with the ZZ phenotype of AAT and emphysema volunteered to participate in the study. Written informed consent was obtained and the study was approved by the ethical board of Leiden University Medical Center. The study consisted of two parts. Firstly, 10 patients (forced expiratory volume in 1 second (FEV_1) <65% predicted) were randomised (1:1) to receive either a single infusion of 250 mg/kg AAT (a dose currently used for monthly infusion) or no treatment. AAT was supplied by Laboratoire Français du Fractionnement et des Biotechnologies, Lille, France. In all 10 patients blood samples were taken on the days indicated in fig 1A. In the second part of the study the other 10 patients (FEV_1 <65% predicted) were randomised (1:1) to receive either two infusions of 250 mg/kg AAT 1 week apart or no treatment and blood samples were taken. In addition, plasma was taken once from 20 healthy controls.

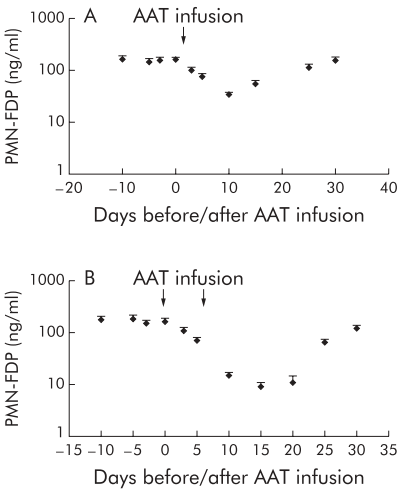

Figure 1 Effect of (A) a single infusion of 250 mg/kg α_1-antitrypsin (AAT, arrow) and (B) two infusions of 250 mg/kg AAT 1 week apart (arrows) on mean (SD) plasma levels of large fibrin(ogen) fragments formed by neutrophil elastase mediated degradation (PMN-FDP).

As shown in fig 1A, the levels of PMN-FDP fragments decreased in patients given the currently used dose but did not reach levels seen in normal individuals. In contrast, doubling the dose of AAT resulted in normal levels of fragments and these levels were maintained for 10 days. PMN-FDP fragments from untreated patients ranged from 109 ng/ml to 179 ng/ml, whereas those from healthy controls ranged from 9 ng/ml to 25 ng/ml.

These results suggest that fibrinogen fragments may serve as a marker for inflammation induced proteolysis in the lung in vivo and that their formation can be inhibited with higher doses of AAT than the currently recommended dose for augmentation. Furthermore, our results suggest that the currently applied dose may not be high enough to produce a protective effect on the decline in lung function in individuals with type Z deficiency of AAT. To justify the cost of this expensive treatment, assessment of the efficacy on the basis of biochemical markers of neutrophil mediated alveolar destruction in these patients is indicated; this is feasible with our assay and other improved assays.[5]

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Authors' reply

Drs Stolk and Nieuwenhuizen present important findings regarding the effect of high dose augmentation therapy on plasma fibrinogen degradation fragments in 20 subjects with PI*ZZ α_1-antitrypsin (AAT) deficiency. Their findings are interesting for two reasons: (1) they examine the effects of doses of augmentation therapy higher than have conventionally been given, and (2) they observed a reduction in PMN-FDP fragments in the group receiving two infusions of augmentation therapy at 250 mg/kg compared with the group receiving a single infusion, thereby supporting the possibility that higher dose augmentation therapy confers benefit.

However, as the authors point out, PMN-FDP is not a specific measure of elastolysis and so, in our view, cannot yet be advanced as evidence of definitive protection against lung destruction in AAT deficiency. Still, their findings invite further study of the dose-response effectiveness of higher dose augmentation therapy, ideally using conventional and emerging measures of lung destruction including detailed pulmonary function tests and chest CT densitometry.

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