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THEMATIC SERIES ''ALPHA-1 ANTITRYPSIN DEFICIENCY''
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Augmentation therapy of alpha-1 antitrypsin deficiency associated emphysema

Traitement substitutif de l'emphysème au cours du déficit en alpha-1 antritrypsine

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Summary
Introduction. — Alpha-1 antitrypsin, secreted by the liver, inhibits neutrophil elastase. Its deficiency favours the development of emphysema. Restoring a ''protective'' serum level in deficient patients should make it possible to inhibit the development of emphysema.
State of the art. — Human plasma-derived alpha-1 antitrypsin is a blood-derived drug sold in France under the name Alfalastin®. The recommended posology is an I.V. administration of 60 mg/kg once a week. Human plasma-derived alpha-1 antitrypsin restores anti-elastase protection in the lower lung and prevents experimental emphysema induced by the elastasis of human neutrophils in hamster. The low number of patients with alpha-1 antitrypsin deficiency is one of the difficulties to perform sufficiently powerful randomised studies. However, randomised studies have reported the efficacy of human plasma-derived alpha-1 antitrypsin perfusions on mortality, FEV1 decline and the frequency of exacerbations. Randomised control trials have demonstrated the efficacy of human plasma-derived alpha-1 antitrypsin perfusions on the loss of lung density assessed by CT scan.

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Conclusion. — Augmentation therapy is simple in its conception and implementation, but it is expensive. However, there are currently no other solutions.

MOTS CLÉS
Alpha-1 antitrypsine ;
Déficit en alpha-1 antitrypsine ;
Administration et posologie ;
Emphysème ;
Protéines du sang

Résumé
Introduction. — L'alpha-1 antitrypsine, protéine sécrétée par le foie, inhibe l'élastase des neutrophiles ; son déficit favorise le développement d'un emphysème. Restaurer chez les malades déficitaires, un taux sérique « protecteur » devrait permettre de ralentir l'évolution de la maladie emphysémateuse.
État des connaissances. — L'alpha-1 antitrypsine plasmatique humaine est un médicament dérivé du sang commercialisé, en France, sous le nom d'Alfalastin®. Il est recommandé de l'administrer par voie intraveineuse à la posologie de 60 mg/kg de poids chaque semaine. L'alpha-1 antitrypsine plasmatique humaine restaure la protection antiélastasique du poumon profond. L'alpha-1 antitrypsine plasmatique humaine prévient l'emphysème expérimental induit par l'élastase des neutrophiles humains chez le hamster. Le petit nombre de malades identifiés comme porteur d'un emphysème par déficit en alpha-1 antitrypsine est une des difficultés pour mettre en place des études randomisées suffisamment puissantes. Des études non randomisées montrent l'efficacité de perfusions d'alpha-1 antitrypsine plasmatique humaine sur la mortalité, le déclin du VEMS et la fréquence des exacerbations. Des études randomisées montrent l'efficacité de perfusions d'alpha-1 antitrypsine plasmatique humaine sur la diminution de la densité pulmonaire analysée par tomodensitométrie.
Conclusion. — Le traitement substitutif est simple dans sa conception et sa mise en œuvre, il est contraignant et coûteux, mais il n'y a pas actuellement d'alternative.

English version

Alpha-1 antitrypsin (α_1-AT) is a liver-derived glycoprotein and the major inhibitor of neutrophil elastase. Its deficiency, a rarely recognised genetic disorder, is a risk factor for pulmonary emphysema caused by free elastase destruction of the lung connective tissue. Augmentation therapy restores antielastase protection and is therefore able to prevent the progression of emphysema.

Alpha-1 antitrypsin deficiency is a frequent autosomic genetic trait

α_1-AT is a liver-produced glycoprotein encoded by the *SERPINA1* gene whose polymorphism is demonstrated by an electrophoretic heterogeneity in a pH gradient (isoelectrofocusing electrophoresis). The various alleles are named according to their migration with the prefix Pi for ''protease inhibitor''. Since PiM is the normal allele, the serum concentration of homozygous PiMM individuals is greater than 1 g/L [1]. PiS and PiZ are the two mutated alleles that are most frequently responsible for the deficiency. Homozygous PiZZ and heterozygous PiSZ patients present with a severe deficiency whereas a moderate deficiency is associated with PiSS and PiMZ phenotypes (or genotypes) (Table 1) [1]. α_1-AT deficiency is the main genetic risk factor for chronic obstructive pulmonary disease (COPD), especially emphysema. The relative risk of developing COPD varies according to the severity of the deficiency (Table 1). The lowest serum concentration value observed in PiSZ individuals, 500 mg/L, is generally considered as a ''protective threshold''. The risk of emphysema is increased with values below this threshold [2]. However, α_1-AT deficiency is very rarely detected in COPD patients [3] even in the presence of emphysema [4]. It is for this reason that α_1-AT deficiency-associated emphysema is rarely identified.

The use of augmentation therapy is based on the pathogenesis of emphysema

α_1-AT is the principal inhibitor of neutrophil elastase [5]. The neutrophil elastase that is released in the alveolar spaces is not inhibited when serum and therefore the alveolar level of α_1-AT are decreased [6]. This leads to degradation of the lung structure and therefore emphysema which is the main complication of α_1-AT deficiency. Smoking increases alveolar elastase activity [5]. As in the case of any disease caused by a decreased concentration of serum protein, augmentation therapy with blood donor plasma derived protein can alleviate the deficiency and restore alveolar antielastase protection, which can inhibit the development of emphysema. The therapeutic hypothesis is that augmentation therapy for α_1-AT deficient patients with emphysema will prevent aggravation of their lung disease.

Proof of this concept dates back to the 1980s

Beginning in the 1980s, the efficacy of augmentation therapy with human plasma-derived α_1-AT was demonstrated by the increased serum and alveolar levels of α_1-AT [2,7]. Human α_1-AT perfusions make it possible to rapidly restore antielastase protection. The α_1-AT serum level remains above the