

Alpha₁-antitrypsin deficiency: A position statement of the Canadian Thoracic Society

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on behalf of the Standards Committee of the Canadian Thoracic Society

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OBJECTIVE: To prepare new guidelines for the Canadian Thoracic Society (CTS) regarding severe alpha₁-antitrypsin (AAT) deficiency and AAT replacement therapy.

MATERIALS AND METHODS: Previously published guidelines and the medical literature about AAT deficiency and AAT replacement were reviewed. The prepared statement was reviewed and approved by the CTS Standards and Executive Committees.

RESULTS: Three studies evaluated AAT replacement. The National Heart, Lung and Blood Institute's AAT Registry was a nonrandomized comparison of patients receiving and not receiving AAT replacement, and evaluated the decline in forced expiratory volume in 1 s (FEV₁) in 927 subjects. The rate of FEV₁ decline was significantly less in those receiving AAT treatment (66 ± SE 5 mL/year versus 93 ± SE 11 mL/year; P=0.03) only in the subgroup with FEV₁ 35% to 49% predicted. In another study comparing 198 German patients receiving weekly AAT infusions and 97 untreated Danish patients, the mean annual decline in FEV₁ was significantly less in treated patients only in the subgroup with FEV₁ 31% to 65% predicted (62 mL versus 83 mL, P=0.04). Neither of these studies was a randomized, controlled study and, thus, cannot be taken as proof of efficacy. A randomized, double-

blind, placebo controlled trial of monthly replacement therapy over three years in 56 exsmokers with severe AAT deficiency and moderate emphysema showed a trend (P=0.07) favouring slower progression of emphysema by computed tomography scan in the group receiving AAT replacement.

CONCLUSIONS: AAT replacement therapy has not been proven definitively to be clinically effective in reducing the progression of disease in AAT-deficient patients, but there is a possible benefit to selected patients. A placebo controlled, randomized clinical trial of AAT replacement therapy is required. The authors recommend reserving AAT replacement therapy for AAT-deficient patients with impaired FEV₁ of 35% to 50% predicted who have quit smoking and are on optimal medical therapy but continue to show a rapid decline in FEV₁, and participation of all AAT-deficient subjects in the Canadian AAT Registry.

Key Words: *Antitrypsin deficiency; Chronic obstructive pulmonary disease; Cirrhosis; Emphysema; Genetics; Screening*

Déficit en alpha₁-antitrypsine : énoncé de position de la Société canadienne de thoracologie

OBJECTIF : Élaborer de nouvelles lignes de conduite à l'intention de la Société canadienne de thoracologie (SCT) concernant un déficit important en alpha₁-antitrypsine (AAT) et le traitement de substitution.

DOCUMENTATION ET MÉTHODE : On a passé en revue des lignes de conduite déjà publiées et la documentation scientifique sur le déficit

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en AAT et le traitement de substitution. Le présent énoncé a été examiné et approuvé par le comité des normes et le Bureau de la SCT.

RÉSULTATS : Trois études ont porté sur la suppléance de l'AAT. La première, celle du registre de l'AAT du National Heart, Lung and Blood Institute, était un essai sans répartition aléatoire visant à comparer un total de 927 patients soumis et non soumis à un traitement substitutif de l'AAT et à évaluer la diminution du volume expiratoire maximal-seconde (VEMS). La vitesse de diminution du VEMS était significativement moins importante chez les patients soumis au traitement substitutif de l'AAT ($66 \pm SE 5$ ml/année contre $93 \pm SE 11$ ml/année, $P=0,03$) seulement dans le sous-groupe dont le VEMS était de 35 à 49 % des valeurs prévues. Dans une autre étude, 198 patients allemands recevant des perfusions hebdomadaires d'AAT ont été comparés à 97 patients danois non traités; la diminution annuelle moyenne du VEMS s'est avérée significativement moins importante seulement dans le sous-groupe dont le VEMS était de 31 à 65 % des valeurs prévues (62 ml contre 83 ml, $P=0,04$). Toutefois, aucune de ces études n'était contrôlée ni hasardisée; elles ne pouvaient donc pas constituer une preuve d'efficacité. Par con-

tre, un autre essai contrôlé contre placebo et mené à double insu avec répartition aléatoire d'un traitement de substitution administré tous les mois pendant trois ans à 56 ex-fumeurs présentant un déficit important en AAT et de l'emphysème modéré a révélé une tendance ($P=0,07$) au ralentissement, démontré par tomodensitométrie, de l'évolution de l'emphysème dans le groupe recevant l'AAT.

CONCLUSIONS : Le traitement substitutif de l'AAT n'a pas prouvé hors de tout doute son efficacité clinique à réduire l'évolution de la maladie chez les patients présentant un déficit en AAT, bien qu'il y ait une possibilité d'effet bénéfique chez des patients sélectionnés. Il est nécessaire de mener un essai clinique contrôlé contre placebo, avec répartition aléatoire, du traitement substitutif de l'AAT. Les auteurs recommandent de réserver le traitement de substitution aux patients qui présentent un déficit en AAT et un VEMS de 35 à 50 % des valeurs prévues, qui ont cessé de fumer et qui, malgré un traitement médical optimal, continuent de connaître une diminution rapide du VEMS. Ils recommandent également l'inscription de tous les sujets atteints d'un déficit en AAT dans le registre canadien de l'AAT.

In 1963, Laurell and Eriksson (1) published a report on their discovery of alpha₁-antitrypsin (AAT) deficiency and its association with emphysema. AAT (now also termed alpha₁-protease inhibitor) is the major component of serum alpha₁-globulin and is the major antiprotease in plasma. Its primary function appears to be inhibition of neutrophil elastase. Severe deficiency predisposes smokers to the development of disabling panlobular emphysema at a relatively young age; most such patients are disabled by the age of 40 years and few survive to the age of 60 years (2,3). The subject has been reviewed in detail in two publications (4,5). Severe AAT deficiency is a relatively common inherited deficiency occurring in about one of 2000 of the Scandinavian population and about one of 6000 of the white population in North America (4). Severe AAT deficiency is estimated to be present in about 1% to 5% of patients with irreversible chronic obstructive pulmonary disease (COPD) who are referred to respiratory specialists.

AAT DEFICIENCY

AAT is a glycoprotein of 394 amino acids (molecular weight 52,000) encoded by a single gene on chromosome 14 (6). AAT is synthesized by the hepatocytes and secreted into the plasma, from which it diffuses passively into the lung interstitium and alveolar lining fluid. Pulmonary macrophages also produce AAT but contribute only a minimal proportion of AAT in the lung interstitial and alveolar lining fluids.

The AAT phenotype is determined by the expression of two codominant alleles classified under the protease inhibitor (Pi) system (4,5). The AAT Pi type is indicated by letters of the alphabet and characterized in the laboratory by the electrophoretic mobility of its two constituent AAT molecules (6). The normal AAT phenotype is MM (medium mobility), while severe deficiency is mostly due to the ZZ phenotype (very slow mobility), in which AAT levels are about 15% of normal (6). The Z phenotype is due to a single amino acid substitution of 342 glutamine to lysine (7). As the result of this single substitution, there are conformational changes in the molecule that prevent its secretion by the hepatocyte due to aggregation of the protein. The heterozygote state

(Pi MZ) occurs in approximately 2% to 3% of the white population, more frequently in those of northern rather than southern European descent (8), and results in AAT levels of approximately 50% to 70% of normal. The MZ heterozygote state may mildly predispose smokers to the development of COPD, although the epidemiological evidence is not consistent (9). Some but not all studies of patients with COPD have noted an increased prevalence of the Pi MZ phenotype (10). In addition, MZ smokers have slightly more abnormalities of lung function than age-matched MM smokers (11). A recent study (12) evaluating AAT genotype in patients undergoing lung resection reported an increased prevalence of Pi MZ in patients with COPD (6% of 193 cases) compared with patients without airflow obstruction (none of 73 cases). Another common variant is the S (slow mobility) allele, which results from an amino acid substitution of 264 glutamine to valine (7). The MS heterozygote state occurs in about 8% of the white population and is more prevalent in southern Europe (8). Individuals with the MS phenotype typically have AAT levels approximately 80% of normal and are not considered to be at increased risk for the development of COPD. About 100 different AAT alleles (including M subtypes) are recognized by the electrophoretic technique of isoelectric focusing, but most are rare. In about one-half of all AAT alleles, the gene variation has been characterized by DNA sequencing (5).

Smokers with severe AAT deficiency are likely to develop disabling COPD in their early 40s (5). The severe deficiency is due to Pi ZZ in approximately 95% of cases. There are more than 20 rare alleles leading to severe deficiency, about one-half of them resulting in no detectable plasma AAT; these are called 'null' alleles. Null homozygotes are at very high risk for the development of emphysema, a risk even greater than that of Pi ZZ individuals. In severe AAT deficiency, emphysema is the predominant lesion and characteristically has a basal predominance, in contrast to the usual tobacco-related emphysema of nondeficient smokers, which is characteristically predominant in the apices. The pathological appearance of emphysema in AAT deficiency is also different from emphysema occurring in the nondeficient smoker, being panlobular or panacinar (involving the whole acinus)

rather than centrilobular or centriacinar (involving the centre of the acinus around the respiratory bronchioles). Symptoms of chronic bronchitis may also be present in 20% to 60% of patients (5). Nonsmokers rarely develop respiratory symptoms before their 50s but may have mild impairment of forced expiratory volume in 1 s (FEV₁) in their sixth or seventh decade of life. Exposure to occupational or environmental pollutants may further predispose patients to the development of COPD. The yearly decline in FEV₁ is greater in smokers than in nonsmokers and is estimated to be between 70 and 100 mL/year (13,14), in contrast to the 25 to 30 mL/year in healthy nonsmokers. In one Scandinavian study of nonsmokers and former smokers with AAT deficiency, the yearly decline in FEV₁ was similar (47 and 41 mL/year, respectively) – intermediate between that of normal nondeficient nonsmokers and that of deficient smokers of 70 mL/year (14). It is likely that impaired lung function is also related to the presence or absence of other inherited factors that have yet to be characterized. Pi ZZ subjects detected in family screening of AAT-deficient emphysema patients have more lung function impairment than Pi ZZ individuals discovered in screening studies of the general population, when cigarette consumption is taken into account (15,16).

All types of emphysema are thought to result from an imbalance between damaging elastases released in the lung and protective antiproteases normally present in lung parenchyma (17). An imbalance favouring elastases leads to proteolytic damage to lung connective tissue, elastin degradation and emphysema. In severe AAT deficiency, the imbalance arises from the inherited deficiency of AAT, the lung's major protective antiprotease, an imbalance that is exaggerated if tobacco smoke simultaneously increases the release of neutrophil elastase in the lung. The aim of antitrypsin replacement therapy is to correct this protease-antiprotease imbalance, and to prevent or slow down the progression of emphysema.

Severe AAT deficiency can also lead to liver disease and the development of cirrhosis (18). The abnormal Z AAT is retained and polymerized in hepatocytes, which may lead to hepatic injury and cirrhosis (19). The diagnosis can be made by liver biopsy, which reveals the presence of intrahepatic, periodic acid Schiff-positive globules due to the retained AAT, as demonstrated by immunohistology. A Swedish study of 120 Pi ZZ infants detected by screening 200,000 newborns found that, although abnormalities of liver function were common, only about 10% of infants had clinically significant symptoms and only a minority (3%) developed cirrhosis (20). Adults with severe AAT deficiency have an increased risk of development of liver cirrhosis and hepatoma (2), but clinically manifested disease is uncommon.

The AAT deficiency state is markedly under-recognized; it is estimated that only about 5% of deficient individuals in the population have been diagnosed (5). Even among patients with COPD, AAT deficiency is underdiagnosed (5). In one survey of 304 individuals with severe deficiency, the average delay between the onset of symptoms and the correct diagnosis was 7.2 years (21); 43% had seen at least three physicians

before the correct diagnosis was made, while 12% had seen between six and 10 physicians. We estimate, based on a prevalence rate of one in 6000 (4), that severe AAT deficiency affects approximately 5000 individuals in Canada, roughly the same prevalence as cystic fibrosis. It is estimated that the deficiency has been diagnosed in fewer than 1000 of these individuals, and only about 60 adults with AAT-deficient emphysema are currently receiving replacement therapy in Canada.

ANTITRYPSIN REPLACEMENT THERAPY

Antitrypsin replacement therapy (22) became available for prescription use in the United States and Canada in 1989. Standard therapy requires weekly infusions of a purified antitrypsin preparation (Prolastin, Bayer Inc, Canada) at a dose of 60 mg/kg (23); monthly infusions of 250 mg/kg have also been used (24). Replacement therapy partially corrects the biochemical defect by raising serum levels of antitrypsin above a theoretically protective threshold level of 0.8 g/L (22-24). This level has been regarded as adequately protective based on the observation that subjects with moderate AAT deficiency (SZ phenotype) who exceed this level appear not to be at a significantly increased risk for the development of emphysema (22). The aim of antitrypsin replacement therapy is to reduce the excessive decline in lung function that these patients experience; replacement therapy is not expected to improve lung function (22).

Prolastin received regulatory approval in North America after clinical trials demonstrated that regular intravenous infusions of the blood product partially and safely corrected the abnormally low levels of AAT typically found in the plasma and bronchoalveolar lavage fluid of deficient individuals. No randomized, controlled clinical trials were done to determine whether such replacement altered the progression of emphysema in deficient individuals; a trial was regarded as unfeasible. It had been estimated that in such a slowly progressive disease, a definitive trial would require the enrollment of 300 to 500 deficient individuals who would then require random assignment between AAT replacement and placebo, and monitoring in a large number of centres over a three-year period (25). The logistics and cost of the study were considered prohibitive. On the basis of the perceived inability to undertake a definitive clinical trial of AAT replacement, and the plausible rationale for benefit indicated by the demonstration of partial correction of the biochemical defect by AAT replacement, the American Thoracic Society (ATS) published its guidelines for AAT replacement therapy in 1989 (22). These guidelines recommended replacement therapy for severely deficient individuals with evidence of significant obstructive lung disease (22), provided that patients had quit smoking and were receiving optimal medical therapy.

In 1992, the Canadian Thoracic Society (CTS) Committee on severe AAT deficiency did not recommend the unqualified clinical use of replacement therapy for severe antitrypsin deficiency with emphysema (26). Instead, replacement therapy was still not considered a definitive therapy and required further study. This stand was taken because clinical efficacy

had not been demonstrated to justify the cost and potential risks of replacement therapy. Antitrypsin replacement therapy is expensive; the cost of a year's supply of AAT for replacement therapy is about \$30,000 (CDN\$), and the nursing costs of intravenous infusions must be added to this figure. The CTS position differed from that of the ATS because of major differences between the American and Canadian health care systems. In Canada, where health care is universal, all patients are potentially eligible for replacement therapy regardless of their ability to pay, while in the United States, only patients whose health insurance covered the cost or who could afford to pay would receive it. We now understand that the development of severe emphysema is not an inevitable consequence of the deficiency state alone. Smokers with AAT deficiency are likely to develop emphysema prematurely, but nonsmokers may develop little or no clinically important lung disease. An important point to consider is that AAT-deficient smokers who have suffered an accelerated decline in lung function while smoking may return to a more normal rate of lung function decline when they stop smoking. It is unclear whether such former smokers continue to need the protection of restored AAT levels once their exposure to tobacco smoke has ended. Finally, there is wide variation among deficient individuals in their risk of developing emphysema independent of their exposure to tobacco smoke. Genetic or environmental cofactors play some role in this variability, but these factors have not yet been fully identified. An understanding of such factors might allow replacement therapy to be targeted to those at greatest risk and might obviate the need for therapy in those at low risk of disease progression.

Evaluating the efficacy of AAT replacement therapy: To obtain information about the natural history of AAT deficiency, the United States National Heart, Lung, and Blood Institute (NHLBI) established a registry of patients with severe AAT deficiency, including patients receiving and not receiving AAT replacement. The baseline characteristics of patients enrolled in the registry were described in 1997 (27). The patients in the registry were not allocated to AAT replacement or no replacement in a randomized fashion, and the registry was not intended as a means of addressing the clinical efficacy of AAT replacement. The follow-up of the 1048 NHLBI Registry patients was published in 1998 (28). Those receiving AAT therapy had decreased mortality (risk ratio 0.64; $P=0.02$) compared with those not receiving replacement therapy. However, there was a potentially confounding effect of socioeconomic status on mortality, given that economic status and, presumably, accessibility to medical care were likely to be better in the patients receiving replacement therapy. Low economic status was shown to be an independent risk factor for mortality in an American epidemiological study of a nationally representative population sample of 3617 adult men and women (29); those in the lowest economic group had a threefold increase in mortality rate compared with those in the highest group. In the NHLBI AAT Registry, the mean decline in FEV₁ in 927 subjects, who had at least two FEV₁ measurements one year or more

apart, was 54 mL/year. Among all subjects, the decline in FEV₁ was not significantly different between those receiving and those not receiving AAT. However, in patients with FEV₁ 35% to 49% predicted, the rate of FEV₁ decline was significantly less in those receiving AAT treatment (66 ± 5 mL/year versus 93 ± 11 mL/year; $P=0.03$). The marked difference in mortality between treated and untreated groups, with only a small difference in FEV₁ decline, raises the possibility that mortality may have been altered by factors other than decline in FEV₁, such as socioeconomic status.

Investigators have exploited the availability of replacement therapy in some European countries but not others to assess the efficacy of replacement infusions. They compared annual rates of FEV₁ decline in 198 German former smokers with AAT deficiency who received weekly AAT infusions with those in 97 AAT-deficient Danish exsmokers who did not (30). The mean annual decline in FEV₁ of 56 mL in the treated group was significantly less than the 75 mL seen in untreated patients ($P=0.02$). However, when the results were stratified according to initial FEV₁ percentage predicted, the difference between treated and untreated patients was significant only in the group with FEV₁ 31% to 65% predicted. Once again, this was not a randomized, controlled study; an editorial regarding this study emphasized the need for a controlled, randomized trial (31).

Investigators have sought more sensitive measures of the progression of emphysema to allow clinical trials of replacement therapy in fewer patients than are allowed by conventional, laboratory-based spirometry. Dirksen and colleagues (32) used daily home spirometry, performed by patients themselves in an attempt to obtain a more precise estimate of FEV₁ decline, in a randomized, double-blind, placebo controlled trial of monthly replacement therapy in Denmark and the Netherlands. A total of 56 Pi ZZ exsmokers with moderate emphysema were randomly assigned to receive either AAT replacement (250 mg/kg every four weeks) or placebo over a period of three years (28). Unfortunately, even with the use of daily spirometry, the determination of the rate of FEV₁ decline was not precise enough to yield a definitive result (32). However, the use of computed tomography (CT) of the chest to quantify the progression of emphysema showed a nearly significant trend favouring a slower progression of emphysema in the group receiving AAT replacement than in the control group ($P=0.07$) (32).

Biochemical assays have been used as indirect means of assessing the efficacy of replacement therapy. Elastin breakdown may be monitored by measurement of urinary excretion of desmosine and isodesmosine, cross-linking amino acids specific only to elastin. Stone and co-workers (33) used high performance liquid chromatography to assay specifically for desmosine and reported an increased excretion of desmosine in both smokers and patients with COPD (34). In a preliminary report (35), they observed that AAT replacement therapy resulted in decreased levels of urinary excretion of desmosine in two patients with severe AAT deficiency, suggesting that the AAT treatment had decreased elastin degradation in these patients. However, additional studies evaluating

urinary desmosine, before and during eight weeks of weekly AAT replacement therapy in 12 patients with severe AAT deficiency, did not show a reduction in elastin degradation (36). A confounding factor in the interpretation of desmosine excretion is that urinary desmosine reflects overall body elastin degradation, while normal lung elastin breakdown accounts for only about 20% of total urinary desmosine excretion.

The availability of replacement therapy in Canada: Only one preparation of purified AAT (Prolastin) is available for intravenous use. There is a worldwide shortage of Prolastin, with production no longer keeping pace with demand as new countries give regulatory approval to the treatment and new patients are identified. To some extent, the shortage is being addressed by plans for additional sites of production and, perhaps, by the development of new and more efficient means of production. As well, other manufacturers are planning commercial production of replacement products. The situation in Canada deserves special mention: the Prolastin that Canadian patients are receiving is not prepared from Canadian blood sources. Although the Canadian plasma that remains after various plasma proteins have been extracted for therapeutic use is potentially available as raw material for the production of Prolastin, it is not being used to relieve the worldwide shortage or to make more of the product available for clinical trials.

For most patients who might benefit from replacement therapy, the practical barrier is payment for the therapy. In one province (British Columbia), replacement therapy is available to individual patients through the Provincial Ministry of Health, which covers a major part of the cost (80% until 1998 and 70% since 1999). Elsewhere, patients can receive therapy only if they have private insurance plans that allow its use or if they are capable of paying for such therapy themselves. This situation is in marked contrast to other blood replacement therapies, such as those for hemophilia; the average patient with hemophilia receives from Canadian Blood Services, without charge, blood products costing approximately \$50,000/year. However, the two deficiency states differ in that, in hemophilia, the manifestations of the deficiency, such as bleeding or hemarthrosis, are more apparent and acute, while in AAT deficiency, emphysema develops slowly over many years and develops in smokers. There is also inconsistency in the availability of diagnostic testing for the disorder. Although all provincial Ministries of Health list measurement of AAT serum levels as an insured benefit, not all of them reimburse laboratories for the phenotyping necessary to confirm the diagnosis and conduct efficient screening of family members.

The AAT used in replacement therapy is prepared from pooled plasma; the plasma units are screened for hepatitis viruses and human immunodeficiency virus, and the purified preparation is heated at 60°C for 10 h to inactivate viruses. The Prolastin preparation is about 80% pure AAT and is only about 50% active (specific activity 0.35 mg functional AAT/mg protein). It has been recommended (22) that patients for AAT therapy be screened for hepatitis B and human immunodeficiency virus, and that they receive hepatitis B vaccine if their screening tests are negative. Replacement

therapy requires regular and frequent infusions to maintain a serum level of AAT above the threshold protective value (22). According to the United States AAT Registry (27), only 53% of patients receiving AAT were receiving it at the recommended weekly interval, about one-quarter were receiving it monthly and one-quarter were receiving it every two to three weeks; only the weekly regimen has been approved by the United States Food and Drug Administration (FDA). A recent study evaluating biweekly replacement therapy showed that it resulted in suboptimal trough levels (37).

AAT replacement therapy is not expected to be helpful if the patient has very severe airflow obstruction. It had been previously suggested that a lower limit of FEV₁ 35% predicted be exceeded before recommending replacement therapy (38). On the other hand, the official ATS recommendations published in 1989 (22) stated that "it is not appropriate to define a lower limit for lung function at this time since it is considered unethical to withhold treatment that may have benefit even in very severe end-stage disease". However, the results of the follow-up evaluation of patients in the National Institutes of Health (NIH) Registry (28) indicated no effect of replacement therapy on FEV₁ decline or on mortality in patients with FEV₁ less than 35% predicted, even though there was a bias favouring replacement therapy as previously discussed. Thus, because of the worldwide shortage of purified AAT available for intravenous replacement therapy, it seems reasonable as a triage at this time to restrict replacement therapy to patients with FEV₁ greater than 35% predicted.

AAT delivered by aerosol therapy has been evaluated in short term studies and has been shown to increase the AAT concentration in the bronchoalveolar lavage fluid in patients with severe deficiency (39). It offers the potential of a more convenient and more economical method of delivering AAT to the lung than intravenous therapy. However, long term safety and clinical efficacy have to be demonstrated by randomized, controlled trials before it is available for clinical treatment of AAT deficiency.

International perspectives: In March 1996, the World Health Organization (WHO) organized a meeting to address the issue of AAT deficiency. The proceedings of the meeting were published in the form of a thorough review, and a set of recommendations for screening and management (5). The WHO recommendations included the following:

All patients with COPD, and adults and adolescents with asthma should be screened once for AAT deficiency using a quantitative test. Those with abnormal results on screening should undergo phenotyping.

Standards of care for AAT deficiency should be developed.

Neonatal screening programs should be undertaken in all developed nations, with appropriate counselling available to deficient individuals identified.

An international AAT deficiency registry should be established.

Randomized, controlled trials of replacement therapy should be conducted, coordinated by an international working party using a multinational, multicentre effort.

Prospects for a randomized, controlled trial: Stoller (40) wrote a thoughtful editorial discussing AAT replacement therapy. He concluded by stating that the “best current evidence certainly supports the clinical efficacy of augmentation therapy, at least in AAT-deficient individuals with moderate airflow obstruction”. He admitted that there are methodological shortcomings and some uncertainty about the clinical efficacy of intravenous AAT therapy. However, he considered that a randomized, controlled trial of intravenous replacement therapy would be unlikely in the United States given the availability of the AAT for clinical use and the acceptance of replacement therapy by the ATS in 1989. However, he noted the possibility of randomized, controlled trials in the United States to assess new formulations or routes of administration (aerosol) of replacement protein, as well as the potential for randomized, controlled trials in other nations. However, more recently, the AAT Deficiency Registry Study Group, with Stoller as a co-author, recommended a randomized, placebo controlled trial to evaluate definitively the efficacy of intravenous augmentation therapy (41). It was calculated that the trial would require 294 patients with FEV₁ 35% to 49% predicted, randomly assigned between treatment and placebo and followed for four years, to detect a difference of 23 mL in the yearly decline in FEV₁ (41). The prospect for a randomized, controlled trial appears more favourable in Europe; except in Germany, Italy and Spain, AAT replacement therapy has not been adopted in Europe. A recent editorial by Stockley (42) reviewed the potential for a controlled trial in Europe, especially using CT scan as the primary outcome measure, which would require a total of only 130 patients to be followed for three years. Although Prolastin is theoretically available for use in Canada, practical barriers limit its availability; a randomized, controlled trial is feasible, particularly if done in collaboration with a European or American study. This presupposes that Canadian blood products will become available to produce additional replacement AAT to be used in a clinical trial. No replacement AAT is currently available for non-clinical use.

CTS RECOMMENDATIONS REGARDING AAT REPLACEMENT THERAPY

In 1992, the CTS Committee on AAT replacement therapy (26) recommended the following: establishment of a national registry for all patients with severe AAT deficiency; a multicentre, placebo controlled clinical trial to document the benefit and safety of replacement therapy before it is regarded as standard therapy; and supportive therapy without AAT augmentation for severe AAT deficiency and emphysema until such data become available. What has happened since 1992 to revise these recommendations?

First, a Canadian National AAT Registry has been created under the auspices of the CTS and in collaboration with an in-

ternational registry. We strongly recommend participation in this registry (Canadian AAT Deficiency Registry; telephone 800-352-8186; Web site www.alpha1canadianregistry.com). All physicians are urged to screen selected individuals for the deficiency. This would include patients with COPD with atypical features such as early onset of disease, positive family history or those who have become disabled in their 50s or 40s, as well as individuals at risk by virtue of a positive family history. Physicians are urged to encourage patients and affected individuals to participate in the registry. Implicit in this recommendation is that provincial health plans must cover the cost of appropriate AAT phenotyping.

Second, two large scale studies – the NHLBI Registry (28) and a German study (43) – have documented the safety of AAT replacement therapy, and studies have suggested a clinical benefit. One controlled study of monthly AAT replacement therapy (32) has reported a borderline effect of AAT replacement in reducing the progression of emphysema by performing CT scan of the chest. Two uncontrolled studies – the NHLBI Registry, comparing treated with untreated patients (28), and the German-Dutch comparative study (30) – suggested a benefit of replacement therapy. However, the nonrandomized nature of these two studies prevents the results from being considered definitive. Taking these three studies (28,30,32) in aggregate, Canadian physicians who counsel patients with AAT deficiency can state that replacement therapy remains an unproven treatment, but there is some evidence suggesting a possible benefit to selected patients (ie, those with FEV₁ 35% to 49% predicted in the NHLBI study [28] and FEV₁ 31% to 65% predicted in the German-Dutch study [30]). In view of the financial restraints on the Canadian health care system – and until more definitive results are shown in a randomized, controlled trial – it is reasonable to restrict the option of AAT replacement therapy to AAT-deficient patients who have an FEV₁ greater than 35% and less than 50% predicted, have quit smoking and are on optimal medical therapy yet continue to show a rapid decline in FEV₁. It is recommended that the annual decline in FEV₁ be determined by comparing the results of at least three spirometric tests obtained after inhaled bronchodilator administration – when patients are clinically stable – at intervals of at least six months (preferably three months) over a period of at least 18 months (preferably two years). Until more definitive international or Canadian Registry data are available, it is suggested that a decline of 80 mL/year or greater be considered a rapid decline, based on data from the NHLBI AAT Registry (28) and the German-Dutch study (30). The report from the NHLBI Registry showed that, in patients with FEV₁ 35% to 49% predicted, untreated patients had a mean decline of $93 \pm \text{SE } 11$ mL/year while treated patients had a mean decline of $66 \pm \text{SE } 5$ mL/year (28). Data from the NHLBI report also indicated that of the 26 patients who never received replacement therapy, approximately 45% had a yearly decline in FEV₁ greater than 90 mL. In the German-Dutch study (30), the difference between treated and untreated patients was significant only in the group with FEV₁ 31% to 65%

predicted; the 112 treated patients had a mean annual decline in FEV₁ of 62 mL (SD 25 mL), while the 58 untreated patients had an annual decline of 83 mL (SD 49 mL) – similar to the data from the NHLBI Registry. If FEV₁ decline had a close to normal distribution, about one-half of these patients would have FEV₁ decline greater than 83 mL/year. Thus, the use of a yearly decline in FEV₁ of greater than 80 mL as a recommendation for augmentation therapy would be expected to result in about one-half of the AAT-deficient subjects with FEV₁ 31% to 50% predicted being considered as candidates for replacement therapy, based on extrapolation of data from these studies (28,30). There is a strong case for treating the rare null homozygotes because they have no detectable AAT and an accelerated decline in lung function.

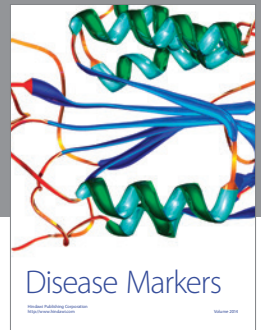
Third, there is growing international consensus about the need for, and feasibility of, a randomized, controlled trial to assess the efficacy of replacement therapy both in the United States (41) and in Europe (42). A placebo controlled trial of replacement therapy over a period of three years is being considered in Europe, using CT scan indication of emphysema progression as the outcome (42). This would require the enrolment of 130 patients to have enough power to show a significant protection against loss of lung tissue (32). We recommend Canadian participation in this study; evaluation of outcome should include not only CT scan and FEV₁ but also assessment of health-related quality of life and physical activity. Implicit in this recommendation is the availability of sufficient purified AAT for replacement therapy to make this possible, perhaps by making Canadian blood products available for the production of purified AAT. Also implicit in this recommendation is the availability of funding for such a randomized, controlled trial to assess treatment of one of Canada's most prevalent genetic deficiency diseases.

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