



September 28, afternoon

“Presentazioni e riflessione”

5 pm *Meet, greet, registration, formalities*

6 pm **WELCOME FROM ALFA EUROPE**

Larry Warren and Nuccia Gatta

6.15 pm **EVERY COUNTRY ASSOCIATION INTRODUCES ITSELF**

Each participating country/group will be expected to give a short presentation (max 10 minutes) to the congress on patients possibilities and problems in their area. This will give us a perspective on the Alpha-1 situation world-wide. Written presentation will be appreciated, this will ensure that we can have a copy for each delegate and important information will not be lost.

7.30 pm **DISCUSSION**

8.00 pm **CHAIRMAN: *Cesare Saltini***

ALPHA1-ANTITRYPSIN DEFICIENCY:

WHERE WE ARE, WHERE WE ARE GOING TO

Maurizio Luisetti

9.00 pm **WELCOME DINNER**

PATIENTS MAY AVAIL OF A SPIROMETRY SERVICE (TANTUCCI'S FELLOWS) WHICH WILL BE ONGOING AND FREE DURING THE CONGRESS.



September 29, morning

“Opening session” - “Conferenza inaugurale”

9.00 am **PATIENTS EMPOWERMENT**
John Walsh

“I perchè”

CHAIRMEN: *Bruno Balbi, Gerry Mc Elvaney*

9.30 am **PATHOGENESIS OF LIVER INJURY IN ALPHA-1-ANTITRYPSIN DEFICIENCY**
Francesco Callea

9.45 am **PATHOGENESIS OF LUNG DISEASE**
David Lomas

10.00 am **THE ASSESSMENT OF LUNG FUNCTION**
Claudio Tantucci

10.15 am **DISCUSSION**

10.30 am **INTERVALLO**

CHAIRMEN: *Maurizio Luisetti, Mark Brantly*

11.00 am **NATURAL HISTORY OF AAT DEFICIENCY IN THE CHILDHOOD**
Eeva Piitulainen

11.15 am **HETEROZYGOUS: A RISK?**
Niels Seersholm

11.30 am **THE NEED OF STANDARDIZATION OF DIAGNOSIS**
Ilaria Ferrarotti

11.45 am **THE IMPORTANCE OF SCREENINGS**
Luciano Corda

12.00 pm **THE ROLE OF REGISTRIES AND PATIENT INVOLVMENT:
THE “PAAIR” PROJECT**
Jan Stolk

12.15 pm **DISCUSSION**

1.00 pm **PRANZO**



September 29, afternoon

“Gli esercizi”

2.30-5.30 pm **“Meet the expert” session**
(one patient to one expert basis)

2.30-5.30 pm **Workshop session**
(three shifting groups for each session)

1. OXYGEN THERAPY
Luca Bianchi

2. LIFE COPING ISSUES
Kitty O'Connor

3. REHABILITATION AND NUTRITIONAL
Francesco D'Abrosca

6.00 pm **CITY TOUR**

9.00 pm **CENA DI GALA**



September 30, morning

“La cura”

CHAIRMEN: *Vittorio Grassi, Claus Vogelmeier*

- 8.15 am **THE CONVENTIONAL TREATMENT OF ALPHA1-ANTITRYPSIN DEFICIENCY RELATED DISEASE**
James Stoller
- 8.30 am **AUGMENTATION THERAPY AND ITS DEVELOPMENT**
Claus Vogelmeier
- 8.45 am **NOVEL THERAPIES FOR ALPHA-1-ANTITRYPSIN DEFICIENCY**
Robert Bals
- 9.00 am **NON PHARMACOLOGICAL TREATMENT OF LUNG DISEASE**
Bruno Balbi

“Closing session” - “Prospettive future”

- 9.15 am **ONGOING RESEARCH AND DEVELOPMENTS**
Robert Stockley and Mark Brantly
- 10.15 am **DISCUSSION**
- 10.45 am **ARRIVEDERCI**
Larry Warren and Nuccia Gatta
- 11.00 am *Transfer to S. Peter Square for Angelus Blessing and Papal audience of the patients*

DURING THE CONGRESS PATIENTS WILL BE ABLE TO WRITE THEIR QUESTIONS TO SPEAKERS: THE QUESTION WILL BE READ BY THE CHAIRMEN.

SPEAKERS, CHAIRMEN AND TUTORS

Bruno Balbi	Veruno	Italy
Robert Bals	Marburg	Germany
Luca Bianchi	Brescia	Italy
Mark Brantly	Gainsville	USA
Francesco Callea	Roma	Italy
Luciano Corda	Brescia	Italy
Francesco D’Abrosca	Veruno	Italy
Nuccia Gatta	Brescia	Italy
Vittorio Grassi	Brescia	Italy
Ilaria Ferrarotti	Pavia	Italy
David Lomas	Cambridge	U.K.
Maurizio Luisetti	Pavia	Italy
Gerry Mc Elvaney	Dublin	Ireland
Kitty O’Connor	Dublin	Ireland
Eeva Piitulainen	Malmo	Sweedan
Cesare Saltini	Roma	Italy
Niels Seersholm	Copenhagen	Denmark
James Stoller	Cleveland	USA
Robert Stockley	Birmingham	U.K.
Jan Stolk	Leiden	Netherlands
Claudio Tantucci	Brescia	Italy
John Walsh	Miami	USA
Larry Warren	Dublin	Ireland
Claus Vogelmeier	Marburg	Germany

ALPHA1-ANTITRYPSIN DEFICIENCY : WHERE WE ARE, WHERE WE ARE GOING TO**Maurizio Luisetti***Center for Diagnosis of Inherited Alpha1-antitrypsin Deficiency
Laboratory of Biochemistry and Genetics Institute of Respiratory Disease
University of Pavia Fondazione IRCCS Policlinico San Matteo Pavia, Italy*

At the beginning of the 1960s, two scientists in Sweden, Laurell & Eriksson, associated missing bands on paper electrophoresis in sera with subjects suffering from pulmonary emphysema and chronic liver disease. This was the first report of a disorder since then referred to as "Alpha1-antitrypsin Deficiency" (AATD). Now, 44 years after the discovery, AATD is in its middle age, and an astonishing amount of data have accumulated during four decades. We have currently a satisfactory view of the AATD epidemiology, at least in western countries; we have gained a good level of knowledge about the pathogenesis of lung and liver disease. We have developed suitable methods for laboratory identification of protein and molecular abnormalities linked to AATD. A number of national registries for AATD have been established, as well as national patient support groups, and their federations work together for a better awareness of the disorder. Replacement therapy is available in a growing number of countries, and several hundreds of AATD subjects with lung disease are currently treated. But a number of relevant questions are still unanswered, and we hope we are able to offer satisfactory answers to these question in the next future. Basic questions, such as the definition of the exact ratio between asymptomatic individuals affected by AATD and individuals affected by AATD which develop lung/liver disease (and, more importantly, what differentiates the latter from the former), and clinical questions, such as the development of more effective "replacement" therapies, are among the questions AATD patients ask the scientific community. This is a commitment for the future.

PATHOGENESIS OF LIVER INJURY IN ALPHA-1-ANTITRYPSIN DEFICIENCY**F. Callea***Department of Pathology Children's Hospital Bambino Gesù Rome, Italy*

Liver pathology is a major manifestation of Alpha-1-antitrypsin deficiency (AAT), restricted to the AAT mutations causing misfolding of the protein and accumulation in the Endoplasmic Reticulum (ER) of hepatocytes.

So far three such mutations have been identified, Z, Mmalton, Siiyama, the Z variant being the most frequent.

The spectrum of the associated liver pathology comprises neonatal cholestasis, chronic hepatitis, cirrhosis and HCC.

The mechanism of the liver damage is not fully understood. There are two major lines of thinking: 1) the storage is toxic per se, 2) additional factors are required for the development of the liver damage.

The main argument favouring the second opinion is mainly based upon the observation that only a minority of AAT deficient individuals develop liver disease.

I would like to emphasize the point that the accumulation of the mutant AAT represents per se the elementary lesion of the disease and that is an unavoidable process.

In this context I will be reviewing the patho-morphogenesis of the storage phenomenon and the main morphological alterations with special regard to new electron microscopic findings. The epidemiological and clinical relevance of the morphological alterations are discussed also in view of the new experimental data on the pathways for degradation of the mutant proteins that accumulate in the ER.

PATHOGENESIS OF LUNG DISEASE**David A. Lomas***University of Cambridge, Cambridge, UK*

Alpha₁-Antitrypsin is produced from the liver and bathes all the tissues of the body. Its role is to protect against tissue damage from enzymes released from neutrophils. The genetic deficiency of alpha₁-antitrypsin that results from the Z mutation causes the protein to form polymers that are retained within the cells of the liver. This retention of protein causes liver disease. The resulting lack of plasma alpha₁-antitrypsin (10-15% of normal levels) leaves the lungs exposed to attack by neutrophil enzymes and so results in emphysema. We have recently shown that some of the alpha₁-antitrypsin that enters the lung can change shape and form chains of polymers. These polymers are unable to function as inhibitors of neutrophil enzymes and so exacerbate the tissues damage. Moreover the polymers are themselves inflammatory and cause further attraction of neutrophils into the lungs. This in turn accelerates the inflammation and emphysema. All these factors are exacerbated by smoking. My laboratory has defined the pathway by which polymers form and is currently developing strategies to block the polymerisation of Z alpha₁-antitrypsin. Such a strategy will prevent the accumulation of Z alpha₁-antitrypsin within hepatocytes thereby treating the associated liver disease. The release of alpha₁-antitrypsin from the liver will increase the circulating levels of alpha₁-antitrypsin and hence provide protection for the lungs against emphysema.

THE ASSESSMENT OF LUNG FUNCTION**Claudio Tantucci***Cattedra di Malattie dell'Apparato Respiratorio, Università di Brescia
Medicina Respiratoria/Prima Medicina, Spedali Civili, Brescia, Italy*

The lung function of subjects with documented alpha1-antitrypsin deficiency (AATD) should be carefully evaluated either to exclude early pulmonary involvement or to detect initial or established alterations; in this case, the lung function testing is very important to assess the severity of lung impairment in order to correctly define the diagnostic picture and the following therapeutic program.

Pulmonary function testing in AATD should include:

- Pre and (if needed) post-bronchodilator spirometry
- Lung volume measurements by helium dilution and body plethysmography
- Single-breath CO lung-diffusing capacity (DLCO)
- Single breath nitrogen wash-out test and, when indicated,
- Arterial blood gas analysis (ABG)
- Exercise testing

Spirometry shows airflow obstruction and quantifies its severity, while the acute administration of a bronchodilating drug permits to see if the obstruction is acutely reversible. Measurement of lung volumes gives indispensable clues about the presence of restrictive defect and air trapping and static and/or dynamic hyperinflation. Single-breath CO lung-diffusing capacity is an index of alveolar septa (and capillary bed) destruction and is very important in AATD because its reduction might be an initial sign of disease and in a patient with lung disorder an important parameter to evaluate the severity of the emphysematous lung dysfunction. Recently, measurements derived by the single breath nitrogen wash-out test have been shown as able to detect alteration of the small airway-lung parenchymal interdependence in AATD patients. ABG provides measures of the efficiency of blood-alveolar gas exchanges and should be done in the presence of advanced lung disease. The study of exertional performance may require incremental or steady-state cardio-pulmonary exercise testing (CPEX) or simpler tests as 6-minute walking test (6MWT) and Shuttle walking test (SWT) that allow useful evaluation of exercise tolerance and oxygen needs.

In subjects with AATD not affected by lung disease, the parameters useful to monitor the lung function in order to early detect lung disease are single-breath DLCO and forced expiratory volume in the first second (FEV1) obtained by maximal full expiratory flow-volume curve.

In patients with AATD affected by COPD (especially due to pulmonary emphysema), the follow-up should be performed by periodical maximal full flow-volume curves to measure the annual decline rate of FEV1, and by ABG and exercise testing. The latter two tests are unavoidable to ascertain the need of long-term oxygen therapy during physical activity (including rehabilitation programs) or at rest.

NATURAL HISTORY OF AAT DEFICIENCY IN THE CHILDHOOD**Eva Piitulainen***Assoc Prof of Respiratory Medicine**Department of Respiratory Medicine and Allergology, Malmö University Hospital, Sweden*

Natural history of severe (PiZZ) and moderate (PiSZ) alpha-1-antitrypsin (AAT) deficiency has been studied in Sweden by screening of all new-born children during November 1972 to September 1974. Among 200 000 children, 122 PiZ (71 boys and 51 girls) and 48 PiSZ (25 boys and 23 girls) children were identified.

A total of 22 PiZ children (18%; 15 boys and 7 girls) had liver abnormalities during the first months of life. Seventeen of them had clinical symptoms of liver disease, while five only had abnormalities in liver function tests. The remaining 98 PiZ children (82%) were healthy. None of the 48 PiSZ children had symptoms of liver disease.

At birth, 10 of the 22 children with liver disease had low birth weight indicating that the liver disease occurs already during the pregnancy. Liver disease was more common among the infants that were breast-fed for less than one month compared with those who were breast-fed for more than one month.

In many children, the liver function tests fluctuated in early childhood in connection with infections (fever) that led to increased levels of liver enzymes, approaching normal range some weeks later.

Since AAT level increases during infections, more mutant protein is formed in the liver during infections and may lead to damage of liver cells. At 16 -18 years of age, none of the PiZ and PiSZ adolescents manifested clinical signs of liver disease but 10% to 15% of them had marginal liver test abnormalities. During the first two years of life, respiratory symptoms were reported in 10% of the PiZ and 2% of the PiSZ children. At 16 years of age, 3% reported that they currently smoked, while 10% were smokers at the age of 18. At 16 and 18 years of age the AAT-deficient adolescents had normal lung function.

Two of the 22 PiZ children having suffered from liver disease died early in childhood from liver cirrhosis, two died from other causes but liver disease was found at autopsy. One PiSZ child died from a sudden infant death syndrome. All remaining AAT-deficient individuals are still alive more than 30 years later.

Conclusion: The Swedish AAT screening study has shown that children with severe AAT deficiency, PiZ, have increased risk of liver disease early in life. Liver disease is more common among boys than among girls. Breast feeding may protect against occurrence of liver disease. None of the AAT-deficient adolescents had clinical signs of liver disease at the age of 18 years. They also had normal lung function.

HETEROZYGOUS: A RISK?**Niels Seersholm***Department of Respiratory Diseases, Gentofte Hospital
DK-2900 Hellerup Denmark*

Is PiMZ a risk factor for the development for COPD? This appears to be a difficult question to answer despite a large number of studies on the subject.

There are a number of reasons for the discrepancy between the studies conducted on this subject. Firstly, smoking is a very significant confounder in the development of emphysema which is almost impossible to control for. Secondly, many studies have been subject to various types of bias particularly selection bias. Thirdly, only a few studies have been sufficiently large to come up with a significant result and very few studies have been population based. And fourthly, the phenotypic appearance of the PiMZ genotype may be heterogenic.

In the studies of a causal relationship of a risk factor (PiMZ genotype) and the development of a disease (COPD) there are two types of designs: case control study and cohort study.

In case control studies the researchers identify a group with COPD, find a proper control group without the disease and compare the prevalence of PiMZ genotype between the groups. This type of study tends to find more PiMZ subjects in the COPD group and thus conclude that PiMZ is a risk factor for COPD. However, this type of study has problems with selection bias and assessment of smoking history.

A typical cohort study follows a group of PiMZ persons and a matched control group over time and compares the number of persons who develop COPD in the two groups. Many of these studies have been negative but the number of participants was often been too small for a firm conclusion.

The ideal study is a large population based study of subjects genotyped at birth and followed up for a life time, but this is very costly and time consuming.

While we await this study we have to advise persons with the PiMZ genotype about their risk for lung disease, and with the current evidence there is no reason to believe they have increased risk as long as they do not smoke.

THE NEED OF STANDARDIZATION OF DIAGNOSIS**Ilaria Ferrarotti***Fondazione IRCCS Policlinico S. Matteo Pavia, Italy*

AATD is a largely under-recognized condition and one of the most common severe hereditary disorders in the world. To improve the diagnostic yield and to address the discrepancy between expected and diagnosed AATD cases, the recently published ATS/ERS Statement (2003) recommends diagnostic testing for all symptomatic adults with emphysema, COPD or asthma with incomplete reversible airflow obstruction, individuals with unexplained liver disease, asymptomatic individuals with persistent obstruction on pulmonary function tests with identifiable risk factors (cigarette smoking, occupational exposure) and adults with necrotizing panniculitis. The laboratory diagnosis of AATD has evolved from the initial description of the condition in 1963 based on paper electrophoresis – agar-gel electrophoresis – immunoelectrophoresis to the currently used methodology, that is a combination of serum AAT level determination, isoelectric focusing (IEF), genotyping, and sequencing. The availability of matrices such as the dried blood spot have facilitated the implementation of laboratory analyses for alpha₁-antitrypsin deficiency, but have also challenged laboratories to develop more reliable and reproducible techniques starting from dried blood.

THE IMPORTANCE OF SCREENINGS**Luciano Corda***Centro Riferimento Deficit Alfa1-Antitripsina**Medicina Respiratoria/Prima Medicina, Spedali Civili, Brescia**Cattedra di Malattie dell'Apparato Respiratorio, Università di Brescia, Italy*

Screening is performed to identify the presence of a disease or a risk factor for a disease, typically among asymptomatic persons. In this way, a disease, or risk factors for a disease, can be detected early, allowing either early treatment or prevention. Screening tests are widely used by clinicians as part of the periodic health examination, as well as by public health officials. Examples of screening tests are as varied as blood tests to detect lead poisoning in young children, mammography to detect breast cancer and questionnaires to identify persons with alcohol or other drug problems.

Even if alpha₁-antitrypsin deficiency (AATD) is considered a rare disease, it is probably the most common widespread genetic abnormality. AATD is rarely diagnosed, both because of poor awareness by health workers and lack of really implemented screening programs. An underrecognition of AATD diagnosis persists in spite of an effort to enhance clinicians' awareness.

From the clinical point of view the under-recognition might be explained by the facts that most of clinical phenotypes associated with AATD are not exclusive to this condition and that the abnormal genes have an incomplete penetrance (the relationship between genotype and clinical phenotype is not strong). The availability of alpha₁-antitrypsin replacement therapy for individuals with pulmonary emphysema associated with AATD encouraged the scientific community to establish and reinforce AATD screening.

Screening for AATD has been recommended by the World Health Organization (WHO) in 1997. The American Thoracic Society (ATS) together with the European Respiratory Society (ERS) in 2003 advice population screening when three main conditions occur: 1) high prevalence of AATD (more than 1/1500), 2) high prevalence of smokers or of people exposed to toxic inhalants 3) availability of an adequate genetic "counselling". A population screening might be very innovative making use of new genetic techniques. An adequate screening program and an early diagnosis of AATD may permit to apply primary (i.e. smoking cessation for lung disease or alcohol abstention for liver disorders) or secondary (i.e. treatment of related lung diseases) prevention measures.

At the moment there are evidences of neonatal screening, patient oriented detection (case-finding) and so called "targeted screening". Recently, the Italian Association of "Alphas" coordinated a screening for AATD in the entire population of a small village in an high risk area.

THE ROLE OF REGISTRIES AND PATIENT INVOLVMENT: THE "PAAIR" PROJECT**Jan Stolk, Laura Fregonese***Department of Pulmonology Leiden University Medical Center Leiden, Netherlands*

The general objective of this proposal is to provide the community at large with an example platform of how patients affected by a rare disease and doctors who need to treat patients with a rare disease can form together a comprehensive set of information in order to contribute to the improvement of the diagnosis, care and treatment of patients with rare diseases. The rare genetic disorder alpha-1-antitrypsin deficiency will be presented as an example of how this general objective can be achieved and improved to reach a higher professional standard. This information may be used by Orphanet, the generalist network on rare diseases in the community (www.orphanet.org), in order to try to achieve similar standards of care and research for other rare diseases. Since 1997, a group of physicians with specific interest in the rare disorder has built a strong network called AIR and since 2005 a group of patients suffering from the rare disorder united in a small group called Alfaeurope.

The strategic objectives are:

- Mapping of new EU countries to check eligibility for membership in the doctors group (AIR) or in patients' organization (Alfaeurope). Compare the standards of the centers already in the AIR network and the centers identified in the new EU countries with the requirements for Reference Centers as defined by the Rare Diseases Task Force working group and adopted by the High Level Group on Health Services and Medical Care.
- To set up interaction between national patient organizations and national doctors/scientists organization (AIR) to generate a model of doctors-patients interaction in three EU member countries, Netherlands, Italy and Germany.
- To establish a European patient organization with legal status for the specific rare condition.
- To investigate the impact of AIR network on morbidity and mortality of the disorder, and on early diagnosis, as compared to what is known from the literature.

This project is necessary to demonstrate the Community that a model of collaboration between doctors/scientists with a specific interest and patient support groups with their own interests will benefit the development of medical care for a rare disorder and that such a model is applicable to other rare disorders in the Community. In fact, in 1996 the World Health Organization in Geneva held an international meeting to clarify the current state of the art in alpha-1-antitrypsin deficiency and to develop recommendations for future work. The meeting indicated that specific research was required to identify the risk factors and clarify the prognosis of lung and liver disease associated with the disorder both in children and adults. In order to bring these recommendations to fruition it was recognized that an international registry was required. In 1998 a provisional database was agreed on and established in Malmo under the direction of Professor S. Eriksson who first described alpha-1-antitrypsin deficiency in 1963. Since then it has been shown that electronic transfer of the basic database is feasible from individual countries and as of 2006 more than 3000 new patients have been added to this registry, in the year 2006 increasing at a pace of 20 newly identified individuals each month.

The partnership is therefore in the unique position to be able to carry this proposal forward.

THE CONVENTIONAL TREATMENT OF ALPHA-1 ANTITRYPSIN DEFICIENCY-RELATED DISEASE

James K. Stoller

Professor of Medicine Cleveland Clinic Lerner College of Medicine

Vice Chairman, Medicine Cleveland Clinic Executive Director, Leadership Development Cleveland Clinic, USA

Severe deficiency of alpha-1 antitrypsin predisposes to several diseases, including emphysema, cirrhosis (liver scarring) and liver cancer, and an inflammatory condition of the skin called panniculitis.

In general, treatment goals are to slow disease progression, enhance survival (where the condition threatens survival), lessen symptoms, prevent exacerbations (e.g., of COPD, etc.), enhance functional status, and improve quality of life.

This paper reviews current recommendations regarding conventional treatment of diseases related to alpha-1 antitrypsin deficiency.

Regarding treating stable chronic obstructive pulmonary disease, the spectrum of available treatments is as follows:

Preventive vaccinations (e.g., influenza, pneumococcal), bronchodilators, inhaled corticosteroids, pulmonary rehabilitation, supplemental oxygen, and surgical options, including lung volume reduction surgery and pulmonary transplantation. Currently experimental approaches such as endobronchial valve placement are beyond the scope of this discussion.

Preventive vaccinations are recommended for individuals with chronic obstructive pulmonary disease. Specifically, the influenza vaccine should be administered once yearly and the pneumonia vaccine administered once before age 65 and a second time thereafter for individuals who lack specific immunodeficiency states. In other special circumstances (e.g., use of chemotherapy, etc.), revaccination with the pneumococcal vaccine is recommended every 5 years.

Bronchodilators are a mainstay of treating chronic obstructive pulmonary disease. So-called beta-agonists, which are bronchodilators, have been established to improve FEV1 (a measure of airflow) and symptoms of breathlessness. Additional evidence suggests that use of long-acting so-called beta-agonist bronchodilators may have benefits as does the combination of a beta-agonist bronchodilator and a so-called anticholinergic bronchodilator, which dilates the airway through a different mechanism. The more recent availability of tiotropium bromide, a long-acting anticholinergic drug, has permitted studies showing that it confers more prolonged bronchodilation and seems to lessen the frequency of exacerbations in patients with chronic obstructive pulmonary disease.

The role of inhaled corticosteroids has become clearer as additional studies have become available. Older randomized controlled trials consistently have shown that inhaled corticosteroids do not change the rate of decline of FEV1 in individuals with COPD but in several studies, the frequency of exacerbations was lessened by regular use of an inhaled corticosteroid. Most recently, the results of the so-called TORCH trial have become available. In this study of combined salmeterol and fluticasone meant to evaluate whether there is any survival benefit associated with regular use of this medication, no statistically significant survival benefit was observed. However, this study confirmed a lower rate of exacerbations among both the inhaled steroid alone and the combined inhaled corticosteroid-salmeterol combination group as well as

a lower rate of decline of FEV1, a result at odds with several earlier randomized controlled trials. Of note, though not defined before the study, there was a higher rate of pneumonia among individuals receiving regular use of the inhaled steroid-bronchodilator, though additional study will be needed to better clarify this surprising finding.

Pulmonary rehabilitation plays an important role in managing patients with chronic obstructive pulmonary disease. Programs consisting of both medical evaluation and treatment, as well as exercise training, education and collaborative self-management and psychologic counseling can be very helpful. Participation in pulmonary rehabilitation has been shown to enhance health-related quality of life and exercise capacity in individuals with chronic obstructive pulmonary disease.

Regarding supplemental oxygen, though no studies have specifically addressed its role in alpha-1 antitrypsin deficiency-related chronic obstructive pulmonary disease, the results of studies in patients with "usual" chronic obstructive pulmonary disease are felt to apply. These studies clearly show a survival benefit from 24-hour use of supplemental oxygen in individuals whose resting room-air PaO2 is below a certain value (55 mmHg) or below a slightly higher value (59 mmHg) if there is evidence of heart strain (so-called cor pulmonale) associated with the low oxygen level. Benefits of using oxygen during exercise relate to enhanced exercise capacity and improved symptoms, though survival benefits of using oxygen during exercise or during the night time only are less evident. Studies are currently under way to further evaluate the benefits of using oxygen in patients whose resting room-air oxygen levels are slightly higher (89-93%) at rest and/or whose oxygen levels fall below 89% with walking.

With regard to surgical treatments, lung volume reduction surgery is a technique to surgically remove the most hyper-inflated or damaged areas of lung in individuals with emphysema. Results of recent randomized-controlled clinical trial (i.e., the National Emphysema Trial [NETT]) have shown that in selected individuals, lung volume reduction surgery can prolong life. Recent results suggest that this survival benefit may persist for up to 7 years of follow-up though, of course, there is a short-term mortality risk of undergoing the surgery itself. In the specific case of alpha-1 antitrypsin deficiency, the benefits of lung volume reduction surgery have been less completely studied, but available research suggests that the benefits are shorter-lived and generally less pronounced than in individuals whose COPD relates to causes other than alpha-1 antitrypsin deficiency. On this basis, it is difficult currently to endorse lung volume reduction surgery for individuals whose COPD is on the basis of alpha-1 antitrypsin deficiency.

Lung transplantation remains an option for individuals whose alpha-1 antitrypsin deficiency has resulted in severe emphysema. Recent collected information from the International Society for Heart and Lung Transplantation indicate that the 5-year survival rate of individuals undergoing lung transplantation for COPD due to alpha-1 antitrypsin deficiency is approximately 50%, with 10-year survival rates of approximately 30%. Compared with other indications for adult lung transplantation, individuals with alpha-1 antitrypsin deficiency are among the most favorable recipient groups, perhaps exceeded slightly by success rates with cystic fibrosis, but exceeding the benefits in patients with idiopathic pulmonary arterial hypertension and those with idiopathic pulmonary fibrosis.

With regard to liver complications of alpha-1 antitrypsin deficiency, no effective medication is currently available. Management of cirrhosis and its complications involves using medications

to diminish the likelihood of bleeding using endoscopic techniques to seal bleeding blood vessels in the esophagus (food tube) and stomach, and using medications such as beta blockers to lessen the likelihood of bleeding from these areas. For individuals with end-stage liver disease, liver transplantation is often recommended. Receipt of a liver from a PI*MM individual also “cures” the alpha-1 antitrypsin deficiency, as serum levels after receipt of a PI*MM liver would be expected to be normal.

Finally, panniculitis is a well-established but uncommon complication of alpha-1 antitrypsin deficiency. Various treatments have been used, including antibiotics, dapson and cyclophosphamide. Among these, dapson seems most widely used with a moderate degree of success. More specific therapy of panniculitis associated with alpha-1 antitrypsin deficiency involves use of intravenous augmentation therapy, which has been associated with rapid clinical resolution of the skin lesions associated with panniculitis.

AUGMENTATION THERAPY AND ITS DEVELOPMENT

Claus Vogelmeier, Robert Bals

Division for Pulmonary Diseases, University of Marburg, Germany

About 20 years ago the first pivotal study on the use of a plasma-derived alpha 1-antitrypsin (AAT) preparation as a therapy for patients with emphysema caused by severe AAT deficiency was published. Patients had received weekly infusions of 60 mg/kg of this AAT preparation. The study demonstrated biochemical efficacy – the AAT levels and the anti-neutrophil elastase capacity in bronchoalveolar lavage increased beyond the threshold considered to be protective. Shortly thereafter, studies with similar endpoints with biweekly and monthly infusions were presented. Later on, data from the American AAT registry and a German-Danish registry suggested that augmentation therapy reduces the loss of lung function over time if baseline FEV1 is between 30 and 65 % predicted. In addition, an observational analysis supported the idea that AAT augmentation may also reduce respiratory infections in patients with AAT deficiency. In 1999 the first randomized trial on the effects of AAT augmentation was published. In this study for the first time lung density as evaluated by CT scans was used as an endpoint. There was a trend in favour of AAT augmentation – patients under augmentation therapy showed a smaller loss of lung density than the placebo group (p=0.07). The patient number (N=56) was too small to come to definite conclusions. Based on this study a bigger multi-centre double-blind placebo controlled study (EXACTLIE) was conducted with the primary endpoint changes in lung density. Currently, the data obtained in this study are evaluated. The results will be presented soon - hopefully giving us a clearer picture with regard to the beneficial effects of AAT augmentation therapy.

NOVEL THERAPIES FOR ALPHA-1-ANTITRYPSIN DEFICIENCY

Robert Bals

Division for Pulmonary Diseases, University of Marburg, Germany

A variety of novel approaches will be available for the treatment of AATD in the future. Some approaches will emerge from the fields of pulmonology and hepatology and target the resulting diseases in AATD such as emphysema or liver cirrhosis. This presentation focuses on novel therapies that aim to correct the basic defect of the disorder and will include:

- Synthetic elastase inhibitors
- Antiinflammatory treatments
- Chaperone-based / small molecule based approaches to prevent polymerization and hepatic release
- Gene therapy
- Therapeutic networks / trial networks

NON-PHARMACOLOGICAL TREATMENT OF LUNG DISEASE**Bruno Balbi***Primario Divisione di Pneumologia Riabilitativa Fondazione Salvatore Maugeri I.R.C.C.S. Novara, Italy*

Lung disease associated with alpha₁ antitrypsin deficiency (AAT-D) is mainly represented by Chronic Obstructive Pulmonary Disease (COPD), although patients may present also with the phenotype of bronchial asthma, bronchiectasis, and pneumothorax. Thus, as for conventional pharmacological treatment, AAT-D patient share with non-AAT-D patients the options available for non-pharmacological treatment of COPD. Those are represented by: 1) Pulmonary Rehabilitation (PR); 2) Lung Transplantation (LTx); and 3) Lung Volume Reduction Surgery (LVRS).

PR is a comprehensive, multidisciplinary non-pharmacological treatment of respiratory disability aimed at restoring the best possible health-related quality of life, at diminishing dyspnoea and at ameliorating the exercise capacity of the individuals. Current guidelines for COPD state that PR is indicated at all stages of COPD when the patient is presenting a significant reduction of daily activities. Unfortunately, given the low numbers of available facilities in- and out-hospital-based, very few patients are offered this possibility. In AAT-D patients, only anecdotal experience are reported in PR. However, it seems logical to suppose that PR may very well be effective also in COPD caused or associated with AAT-D as it has been demonstrated for non-AAT-D COPD.

LtX is an option that has been increasingly adopted in various end-stage lung diseases as well as in pulmonary vascular disorders. The rates of LTx vary from Country to Country due to many logistical, cultural, social, economical factors. Considering the data from the International Society from Lung and Heart Transplantation, AAT-D patients represent the fourth leading cause of this procedures, being COPD, Idiopathic Pulmonary Fibrosis, and Cystic Fibrosis the first three. This is important as it outlines the fact that usually AAT-D patients are good candidates for LTx, being younger and less compromised as compared with other patients. Unfortunately, not all Countries select patients also on the basis of their genetic condition, e.g. in Italy no data are available for AAT-D COPD patients in Lung Transplant National Registry.

LVRS has been very popular some years ago, until a study involving a large number of subjects showed that more compromised patients undergoing LVRS are at higher risk than other patients, as it is probably also for AAT-D patients. This restricted significantly the indications of LVRS. Recently another option was put forward for advanced COPD: the “endoscopic” LVRS by means of unidirectional valves placed endoscopically in the airways. It should be underlined that both LTx and LVRS are aimed more at increasing quality of life than at prolonging patients’ lives.

ONGOING RESEARCH AND DEVELOPMENT**Robert Stockley***University Hospital, Birmingham, U.K.*

From the first recognition of alpha₁ antitrypsin deficiency in 1963 the research field became very active exploring the deficiency as a cause of all COPD. In the early 1980s augmentation therapy was introduced and with the understanding that this was “a cure” research activity waned.

However in recent years a more inquisitive approach to the condition has emerged. Why do some AATD patients remain well? How does the lung disease present? How does it develop? How should patients be treated? What is the effect of chest infections? Can we prevent deterioration? Can we repair the damage? These and many other questions challenge us for the next few years.

Of importance clinical trials of old or new treatments will emerge and be delivered through the extensive collaboration of researchers and the developments of the AIR and AOF registries. However it is critical that these are co-ordinated and not replicated merely to appease regulatory bodies. Close collaboration between medical registries, pharmaceutical companies and patient groups will be essential if we are to assess future therapies adequately.