

## Proposed Programme

**TITLE:** Management of patients with Asthma & COPD: Beyond FEV1

**VENUE:** Auditorium Paganini

**DATE:** May, 29th 2009

### **EDUCATIONAL AIM OF THE EVENT:**

Chronic respiratory diseases represent a wide array of serious diseases and constitute a serious public health problem in all countries throughout the world. They include asthma (300 million) and respiratory allergies, chronic obstructive pulmonary disease (COPD) (80 million moderate/severe COPD), occupational lung diseases and pulmonary hypertension.

Asthma is one of the most common chronic inflammatory disorders of the airways characterized by recurrent episodes of airflow limitation and by acute exacerbation that can be gradual or rapid in onset. It is a debilitating condition that affects both children and adults and can severely disrupt everyday life.

Chronic obstructive pulmonary Disease (COPD) is a preventable and treatable disease characterized by airflow limitation that is usually progressive, associated with an abnormal response of the lung to noxious particles or gases. It is not fully reversible and produces some significant extra pulmonary effects that may contribute to the severity in individual patients.

In the light of the recent scientific interest towards complementary approaches to spirometry (i.e. FEV1) in the management of patients with asthma and COPD, this year edition of the Respiration Day is focused on the importance of merging the information coming from lung function tests together with patients related outcomes, biomarkers and imaging. Particularly, these last two parameters are of great interest for the investigation of the different pulmonary areas, included the small airways.

The congress will open with an integrated overview of the topics that will be discussed in detail in the following talks. The afternoon session will give the opportunity to see how the concepts discussed in the morning may have a practical application in clinical practice.

### **APPROPRIATE PARTICIPANTS:**

Estimated participants: around nr. 586 guests, pneumologists and all specialists in respiratory medicine.

- nr. 126 Italy
- nr. 27 France
- nr. 30 Spain
- nr. 52 Germany
- nr. 105 Turkey
- nr. 17 Austria
- nr. 4 Brasile
- nr. 26 Medio Oriente
- nr. 12 Maghreb
- nr. 5 Korea
- nr. 30 Holland
- nr. 40 Uk
- nr. 54 Greece
- nr. 46 Cz, Poland, Romania, Russia, SL, SK
- nr. 12 Relatori (USA, Belgium, Greece, Italy, Germany, Netherlands, France, Spain)

## **SCIENTIFIC PROGRAMME**

***“Management of patients with Asthma & COPD: Beyond FEV1”  
Parma, Auditorium Paganini – 29th May 2009***

**President: Prof. Dario Olivieri**

**09.00 Introduction and Welcome**

*Dario Olivieri, Italy*

**09.00-10.00 Similarities and differences between Asthma and COPD**

*P. Barnes, UK*

**10.00-13.15 Morning Session**

Chairmen: J. Bousquet, France / H. Magnussen, Germany

**10.00-10.30 Lung function tests beyond FEV1**

*L.M. Fabbri, Italy*

**10.30-11.00 Biomarkers in Chronic Respiratory disease**

*A. Augusti', Spain*

**11.00-11.10 Discussion**

*11.10-11.30 coffee break*

**11.30-12.30 Patient Related Outcomes:**

***Asthma***

*P.M. O'Byrne, Canada*

***COPD***

*T. Trooster, Belgium*

**12.30-13.00 The role of imaging in Asthma and COPD**

*E.A. Hoffman, USA*

**13.00-13.15 Discussion**

*13.15 Lunch*

**14.30-16.30 Managing patients with Asthma & COPD: hints for clinical practice**

*Chairman: L.M. Fabbri, Italy*

### ***Asthmatic patient – Decision making flow***

*M. Kraft, USA*

### ***COPD patient – An integrated approach***

*N.M. Siafakas, Greece*

### ***Pulmonary Involvement in other chronic conditions***

*K. Rabe, The Netherlands*

**16.30-16.45** *Summing Up*

**16.45-17.00** *Evaluation Test*

## **ABSTRACTS**

### **SIMILARITIES AND DIFFERENCES BETWEEN ASTHMA AND COPD**

***Peter Barnes, Imperial College London, UK***

Both asthma and COPD involve chronic inflammation of the respiratory tract that leads to airflow limitation and respiratory symptoms and it has been argued that they are both different manifestations of the same disease process (Dutch hypothesis). However, there are marked differences in the inflammatory process in these diseases, with involvement of different cell, mediators, different consequences and different response to treatment. Some patients with COPD also have features of asthma, however as both diseases may coexist in the same patient.

#### **Pathology**

Asthma is a disease of variable bronchoconstriction due to the intermittent and triggered release of several bronchoconstrictor mediators. Structural changes (airway remodelling) also occur with time, including subepithelial fibrosis (present even in very mild disease), airway smooth muscle hypertrophy and hyperplasia, angiogenesis, mucus hyperplasia and airway fibrosis. Asthma usually involves large airways but in more severe disease extends to involve small airways. By contrast, COPD involves mainly small airways and lung parenchyma. Airway obstruction is due to fibrosis and thickening of small airways and loss of alveolar attachments so that airways close on expiration trapping air and leading to hyperinflation and exertional dyspnoea.

#### **Inflammation**

Both asthma and COPD involve many different inflammatory cells types, with the consequent release of multiple different and differing mediators. In asthma there is an activation of surface mast cells, which release several bronchoconstrictor mediators such as histamine, leukotriene D<sub>4</sub> and prostaglandin D<sub>2</sub>. There is usually an infiltration of eosinophils, orchestrated by CD4<sup>+</sup> Th2 cells, which release the Th2 cytokines IL-4, IL-5, IL-9 and IL-13. IL-4 and IL-13 stimulate B cells to release IgE to sensitise mast cells which are enhanced by IL-9 and stem cell factor. Dendritic cells play a key role in asthmas and regulate Th2 cells via the chemokine TARC acting on CXCR4. Dendritic cells release thymus stromal lymphopoietin, a key upstream cytokine. In COPD there is a different pattern of inflammation, with recruitment of neutrophils, increased numbers of macrophages and a predominance of CD8<sup>+</sup> Tc1 cells (but Th1 cells are also increased). Regulatory T cells (Tregs) may be defective in asthma and COPD. Dendritic cells or mast cells do not seem to play a key role in COPD. There is fibrosis round small airways and TGF-β is believed to play an important role, but smooth muscle hypertrophy is not seen as in asthma. There is alveolar wall destruction (emphysema) with loss of elastic fibres due to an imbalance between elastases and antiproteases; CD8<sup>+</sup> cells may also contribute to alveolar wall destruction via apoptosis of alveolar wall cells.

#### **Response to therapy**

Most asthma patients are very responsive to small doses of corticosteroids, with effective suppression of inflammation. However, patients with COPD are poorly responsive even to very high doses of corticosteroids. Thus corticosteroid resistance appears to be due to oxidative stress and reduced activity and expression of

histone deacetylase-2 (HDAC2), a key nuclear enzyme which mediates the effects of corticosteroids in switching off multiple activated inflammatory genes.

### **Transcription factors**

Several transcription factors regulate the inflammation in asthma and COPD. NF- $\kappa$ B is activated in asthma and COPD and regulates the expression of multiple inflammatory genes. In asthma GATA-3 in Th2 cells plays a key role in orchestrating allergic inflammation.

### **Severe asthma similar to COPD**

Although there are marked differences between mild asthma and COPD, patients with severe asthma have many features similar to COPD. For example there is an increase in neutrophils in the airways, there may be activation of CD8+ and Th1 cells and mediators such as TNF- $\alpha$  and CXCL8 become predominant. There is also an increase in oxidative stress as in COPD and this may contribute to the poor responsiveness to corticosteroids. Asthmatics who smoke also have increased neutrophilic inflammation, oxidative stress and lose their responsiveness to corticosteroids. IL-17 may be an important mediator of neutrophil inflammation in asthma and COPD and is released from specific Th17 cells that are regulated by IL-23.

### **What does this mean for drug development?**

Different treatments are needed for mild asthma and COPD, whereas severe asthma, which shares many features with COPD, may respond to the same anti-inflammatory therapies that will work in COPD. There is less need to new treatments for mild asthma as inhaled LABA/steroid combination therapy is so effective, but a pressing need for drugs that effectively suppress the inflammation in COPD and severe asthma and reverse the structural changes in both diseases.

### **References**

Barnes PJ. Cytokine networks in asthma and chronic obstructive pulmonary disease. *J Clin Invest* 2008; 118:3546-56.

Barnes PJ. Immunology of asthma and chronic obstructive pulmonary disease. *Nat Immunol Rev* 2008; 8: 183-92.

## **LUNG FUNCTION TESTS BEYOND FEV1**

**Leonardo M. Fabbri**

The primary outcome assessment for diagnosis and response to therapeutic interventions in asthma and COPD has been primarily forced expiratory volume in 1 second (FEV1), but this has several limitations. Other pulmonary function testing via spirometry can be particularly useful in addition to FEV1 and may be related with specific pathophysiological abnormalities. In asthma, forced vital capacity (FVC) and slow inspiratory vital capacity (SVC) are parameters that may contain important information on the functioning of small airways. In COPD, validity and reproducibility of FEV1 is still a challenge and studies have shown that other physiologic parameters, such as forced vital capacity (FVC), inspiratory capacity (IC), residual volume (RV), and functional residual capacity (FRC), may be more sensitive for detecting response to various pharmacologic interventions, also because they may better reflect distal lung physiology.

## **BIOMARKERS IN COPD**

**Alvar Agusti**

Chronic obstructive pulmonary disease (COPD) is a heterogeneous disease. Although it has been and still is defined by the presence of non-fully reversible airflow limitation, COPD has many components, both in the lungs and outside them, that are not always captured by the spirometry. The presence of bacterial colonization, airway inflammation, emphysema (to name only a few pulmonary domains of COPD) as well as skeletal muscle dysfunction, cardiovascular morbidity and/or osteoporosis (to name a few extra-pulmonary

manifestations of the disease) are good examples of important aspects of the disease that go well beyond FEV1. Because of this heterogeneity, there is interest in identifying different biomarkers that can help investigators to dissect different phenotypes of the disease, clinicians to improve their prognosis capacity and guide their therapeutic recommendations, and industry to better define the target population of their products as well as to improve the efficiency of the entire drug development process. This presentation will review some relevant aspects of biomarkers in COPD.

***PATIENT RELATED OUTCOMES: ASTHMA***

***Paul O'Byrne***

Asthma is a chronic disease that can be debilitating for patients and costly from an economic and social perspective. The complex nature of asthma and of its response to treatment makes pulmonary function tests alone not sensitive enough to fully describe the health status of an asthmatic patient and warrants a combined approach to identify and monitor patients with uncontrolled or difficult-to-treat asthma. This approach requires the incorporation of patient-reported outcomes (PROs), in order to integrate "physiological" outcomes with "quality of life" data obtained by questioning the patients before and after drug intake. For this reason PROs are increasingly used in both clinical trials and clinical care to evaluate patient benefits. Different tools, such as the Asthma Control Questionnaire (ACQ), the Asthma Control Test (ACT) and the Asthma Quality of Life Questionnaire (AQLQ) are currently being validated. The purpose of this review is to identify currently available PROs for patients with asthma and to make recommendations regarding future development and application of these measures.

***PATIENT RELATED OUTCOMES: COPD***

***Thierry Troosters, Universiteit Leuven***

COPD is a very prevalent disease in western society causing significant morbidity and mortality. For years therapy was limited since COPD was defined as an 'irreversible' lung disease. Nowadays, however it is known that although the disease is indeed only partially reversible, patients do benefit significantly from interventions. In several diseases, and COPD in particular, single physiological end points (such as lung function) only weakly relate with the perceived benefits of interventions in patients. Two extreme examples are given to illustrate this: 1) pulmonary rehabilitation does significantly improve health related quality of life, exercise performance and physical activity, without altering lung function in COPD<sup>1</sup>. On the other hand, patients after lung transplantation may have normal lung function, but their exercise capacity and physical activity levels remain significantly impaired<sup>2</sup>. These are just two extreme examples, but also with pharmacotherapy discrepancies have been observed between the effects on some physiological end points and the spin-off in terms of outcomes that are more relevant to patients.

This discrepancy between single physiological and points and perceived benefits of interventions has prompted regulatory authorities to request proof of our interventions on outcomes with immediate importance to patients. Examples of such outcomes are health related quality of life questionnaires or symptom reports directly obtained from patients. A specific form of patient centered outcomes are 'patient reported outcomes' (PRO's). A PRO is a measurement of any aspect of a patient's health status that comes directly from the patient (i.e., without the interpretation of the patient's responses by a physician or anyone else)<sup>3</sup>. In order to qualify as true PRO's these need to follow a rigorous validation process which essentially starts by obtaining information from patients in qualitative studies. Recently the EXACTPRO initiative developed a PRO targeting the impact of exacerbations of COPD<sup>4</sup>. More recently a European consortium including academic partners, patient and scientific associations and the Pharma-industries has joined forces in the European Innovative Medicines Initiative to develop a PRO aiming at assessing relevant dimensions of physical activity in patients with COPD (PROactive). Physical activity is indeed an important patient centered outcome and can only be comprehensively assessed with a PRO. Enhanced physical activity is important as it is essential for healthy aging<sup>5</sup> and clearly contributes to quality of life.

Reference List

1. Troosters, T., R. Casaburi, R. Gosselink, and M. Decramer. 2005. Pulmonary Rehabilitation in Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 172:19-38.

2. Maury, G., D. Langer, G. Verleden, L. Dupont, R. Gosselink, M. Decramer, and T. Troosters. 2008. Skeletal muscle force and functional exercise tolerance before and after lung transplantation: a cohort study. *Am.J.Transplant.* 8:1275-1281.
3. U.S.Food and Drug Administration. Guidance for Industry: Patient reported outcomes: use in medical product development to support labeling claims. Draft, 1-32. 2006. Rockville, Office of training and Communications.
4. Jones, P. and T. Higenbottam. 2007. Quantifying of severity of exacerbations in chronic obstructive pulmonary disease: adaptations to the definition to allow quantification. *Proc.Am.Thorac.Soc.* 4:597-601.
5. Booth, F. W., M. V. Chakravarthy, S. E. Gordon, and E. E. Spangenburg. 2002. Waging war on physical inactivity: using modern molecular ammunition against an ancient enemy. *J Appl.Physiol* 93:3-30.

## ***THE ROLE OF IMAGING IN ASTHMA AND COPD***

***Eric A. Hoffman***

With the promise of genotype associations serving to differentiate Asthma and COPD patients into distinct and varied pathologies, imaging is serving as a tool to help identify important phenotypes aiding the search for the underlying genetic variations. Similarly, drug discovery processes, safety testing, outcomes assessment and definitions of study populations are all beginning to utilize imaging as a basis for progress in the quest to treat, halt progression, and potentially reverse and cure here-to-fore deadly pathologic processes. The past four decades have seen the progression of x-ray CT imaging from single slice scanners, capable of imaging a single slice in a matter of a few seconds to now imaging the whole lung from apex to base in under a second with sub-millimeter, isotropic voxel resolution. From these images, the lungs, lobes, airways and vascular tree are extracted and interrogated quantitatively by computer processes, parenchymal characteristics are classified and quantified via assessment of simple density distributions or through the objective assessment of complex mathematical patterns buried in the regional brightness variations within the image. Dynamic imaging of the passage of a sharp bolus of contrast agent through the lung field provides regional measures of regional parenchymal perfusion parameters with the possibility of deconvolving the signal so as to provide indices of the timing of flow through the microvascular bed at the very interface of gas exchange, and non-radioactive xenon gas is serving as an x-ray contrast material yielding measures of regional ventilation with the same fine resolution as achieved for perfusion. Recently, a second x-ray tube has been introduced onto a 128 slice CT scanner, allowing not only for the spiral scanning of the entire lung in 0,6seconds, but also for the use of dual energy imaging which allows for the decomposition of the reconstructed image into multiple components including xenon, iodine and the resident body tissues, providing clinical viability of methodologies to rapidly assess regional lung structure and function during a single of a few rapid breath holds and the possibility of producing a "virtual" non-enhanced as well as a contrast enhanced image from a single scan. New magnetic resonance imaging methods are employing hyperpolarized helium or xenon gas to provide needed signal in an organ system typically devoid of enough protons for MR exploration. The scanner is re-tuned to listen to the relaxation of the hyperpolarized gas, with the result being a quantitation of peripheral lung air space size (Apparent Diffusion Coefficient), and the assessment of regional ventilation or the lack there-of. Conventional proton imaging along with the use of gadolinium contrast agent provides a measure of regional perfusion. The polarized xenon gas signal changes when the gas is in its free state in the alveoli vs. when the gas transfers into the alveolar wall and then into the blood, thus yielding indices of the timing of the gas transfer process.

With the above imaging capabilities we now have the means of assessing, for instance, airway remodeling, regional air trapping or the alteration of the hypoxic vasoconstrictor response in the presence of inflammation. Such measures provide important new phenotypes that may very well, in themselves, represent important clues as to the etiology of the disease itself, not just the manifestation of end points of pathologic processes. Armed with these sorts of information, pharmaceutical interventions can be devised and tested; endobronchial explorations and interventions can be guided. These tools are being used in numerous government and private industry sponsored research programs and multi-center trials in the field of COPD and Asthma research. In this talk, we will explore the new scanning methodologies and the information they are providing with particular foci on Asthma and COPD.

Background reading:

Hoffman EA, Simon BA, McLennan G. State of the Art. A structural and functional assessment of the lung via multidetector-row computed tomography: phenotyping chronic obstructive pulmonary disease. Proc Am Thorac Soc. 2006 Aug;3(6):519-32.

Busacker A, Newell JD Jr, Keefe T, Hoffman EA, Granroth JC, Castro M, Fain S, Wenzel S. A multivariate analysis of risk factors for the air-trapping asthmatic phenotype as measured by quantitative CT analysis. Chest. 2009 Jan;135(1):48-56.

Aysola RS, Hoffman EA, Gierada D, Wenzel S, Cook-Granroth J, Tarsi J, Zheng J, Schechtman KB, Ramkumar TP, Cochran R, Xueping E, Christie C, Newell J, Fain S, Altes TA, Castro M. Airway remodeling measured by multidetector CT is increased in severe asthma and correlates with pathology. Chest. 2008 Dec;134(6):1183-91.

### ***ASTHMATIC PATIENT – DECISION MAKING FLOW***

***Monica Kraft, M.D.***

Asthma is a disease characterized by cough, wheezing and shortness of breath. The symptoms can be non-specific, and thus many processes are called asthma that ultimately are not. The process of diagnosing asthma begins with a careful history, a knowledge of the differential diagnosis, and measurement of lung function, a critical aspect of the evaluation. The use of methacholine challenge can be helpful if the diagnosis is in question. The evaluation of contributing factors such as sinusitis/rhinitis, gastroesophageal reflux disease, obstructive sleep apnea and vocal cord dysfunction cannot be underemphasized, as these processes alone can mimic the signs and symptoms of asthma.

Once the diagnosis is suggested, the emphasis in therapy is assessment of severity initially, followed by a focus upon asthma control. Both of these measures incorporate the FEV<sub>1</sub>, prevalence of nocturnal symptoms, rescue inhaler use and assessment of risk, the latter manifested by the number of exacerbations per year. The process of selecting therapies and assessing control is well described in both the GINA and NHLBI guidelines, which will be discussed, and involves stepping therapy up and down depending on degree of asthma control. There are also several ways to assess control easily, via questionnaires such as the Asthma Control Questionnaire or the Asthma Control Test. These questionnaires, in addition to periodic measurement of lung function and assessment of risk can assist the clinician in quickly assessing control so that decisions regarding stepping up or down therapy can be made.