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RESPIRATORY

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INSIDE

Review of

ERS 2014

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Respiratory

Editor-in-Chief: Dr Nikolaos M. Siafakas

Professor of Thoracic Medicine, Department of Thoracic Medicine, University General Hospital, Medical School, University of Crete, Crete, Greece; European Respiratory Society Past President (2009-2010).

Welcome

Prevention, education, and innovation are three concepts which every respiratory specialist needs to incorporate into their daily practice; it is through these measures that the burden of lung disease may be prevented. The *European Medical Journal Respiratory* combines all these concepts in order to update respiratory specialists through peer reviewed articles, congress reviews, and news stories covering the most recent developments within this speciality.

In order to reduce the burden of lung disease, the European Respiratory Society (ERS) and the European Lung Foundation (ELF) have joined forces to forge the Healthy Lungs for Life campaign. This campaign hopes to raise awareness and knowledge of lung conditions and ways to prevent lung damage. Moreover, the campaign hopes to reduce the number of people suffering from respiratory diseases.

In our 'Congress Review' section we have detailed the findings of the ESCAPE study which supports the ERS/ELF campaign. The study found that a high level of air pollution meant that there was a decline in overall lung health. In 2012, 7 million deaths occurred due to air pollution; of these, 3.7 million deaths were attributed to poor outdoor air quality. Thus, there is an urgent need to educate people concerning the importance of clean air.

In addition to this, Dr Upadhyay et al. suggested, in their paper *'Inhaled ambient particulate matter and lung health burden,'* that increased ambient particulate matter (PM) is related to a variety of cardio-respiratory disorders, including chronic lung disease. The authors focused their paper on epidemiological, clinical, and experimental findings, and found that hazard or toxicity criteria of air pollutants, exposure characteristics, and an environmental risk evaluation are needed to understand both the sensitivity and susceptibility of exposed individuals.

Chronic obstructive pulmonary disease was another topic discussed during the Congress. The *Aerobika*® Oscillating Positive Expiratory Pressure Therapy System may prove to be a relief for suffers of this condition. This innovative hand-held device addresses the need to clear patients of mucus. Similarly, in our 'What's New' section, we feature a story concerning Anoro®, a new treatment which may be a viable alternative for patients in whom dual bronchodilator treatment in a single inhaler may be appropriate.

Dr Sohal et al., in their paper: *'Novel insights into chronic obstructive pulmonary disease (COPD): an overview,'* suggests that there needs to be a better understanding of the respiratory host-pathogen relationship; by doing this, it will enable better translational treatments and management strategies to be developed.

The *EMJ Respiratory* journal is home to the latest news within this diverse area and it is our hope that we can have a positive impact upon both your practice and your patients. It is with this sentiment that I wish you a very pleasant read.

Spencer Gore

Director, European Medical Journal

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Foreword

Prof Nikolaos Siafakas

Department of Thoracic Medicine,
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Dear Colleagues,

Becoming the first Editor-in-Chief of a new medical journal has never been an easy job. Succeeding a very successful first contributor, Professor Nicholas Hill, makes the job even more difficult! He introduced the inaugural volume of *EMJ Respiratory* and defined its aims and ambitions. As his successor, I would follow the same pathway by encouraging both novice and experienced researchers alike to submit comprehensive reviews and to be a part of this dynamic and rapidly evolving journal.

The journal has focused on the recent advances in the pulmonology field by publishing balanced reviews and practical guidelines. The journal aims to keep the busy clinician and industry professional up-to-date on the recent developments in this diverse field. The journal strives to cover all major fields of clinical pulmonology such as: airway diseases, lung infections, interstitial lung diseases, lung malignancies, and smoking-related diseases.

In addition, the EMJ staff have attended the largest respiratory event in Europe and have reported on the most interesting and innovative developments in the pathophysiology, management, and primarily in the development of new drugs or new modes of treatment for these respiratory diseases. The Annual European Respiratory Society (ERS) International Congress, which took place in Munich, Germany from 6th-10th September 2014, is featured as a major highlight in the journal, showcasing a wide and valid source of new developments in respiratory medicine. This well-known Congress fully covered, on one hand, basic science and, on the other, clinical respiratory medicine through its impressive scientific programme.

I wish to thank the Editorial Board of *EMJ Respiratory*, the well-known experts in Pulmonology, for their efforts to guide the first two issues and I do hope that they are going to continue to support the journal in the upcoming years.

Finally, I would also wish to congratulate the staff of the publishing company, who are extremely skillful and made the launching of the *EMJ Respiratory* so successful. The challenge ahead is to continue the success story of this young journal by attracting high quality scientific papers and reaching the most prestigious readers.

I wish you all a pleasant and informative read.

Kind regards,

Nikolaos Siafakas

Professor of Thoracic Medicine, Department of Thoracic Medicine, University General Hospital, Medical School, University of Crete, Crete, Greece; European Respiratory Society Past President (2009-2010).

ERS ANNUAL CONGRESS 2014

ICM-MESSE MÜNCHEN
MUNICH, GERMANY
6TH-10TH SEPTEMBER 2014

Welcome to the *European Medical Journal* review of the European Respiratory Society Congress 2014

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Welcome to the *European Medical Journal* review of the European Respiratory Society Congress 2014

The 24th International Congress of the European Respiratory Society (ERS) was held from 6th-10th September 2014 in the exquisite city of Munich, Germany. The pure essence and serenity that exude from this city make it the ideal backdrop for this highly esteemed Congress.

Nestled in the heart of Bavaria, Munich continues to be a modern and cosmopolitan city with a rich heritage, tranquil atmosphere, and stunning architecture. The largest collection of science and technology masterpieces from the early beginnings to the present day can be found in the spectacular Deutsches Museum.

This city was home to Prof Wilhelm Conrad Röntgen, a German physicist who discovered X-rays in 1895 which became a great revolution in the fields of physics and medicine, and earned him the first Nobel Prize in Physics in 1901. To this day, a chest X-ray scan is the first point of contact for healthcare professionals in the evaluation and diagnosis of a wide range of respiratory conditions. With this legacy in mind, researchers will continue to push the boundaries on further scientific discoveries.

This year's Congress saw the launch of the Healthy Lungs for Life initiative and theme of 'Breathe Clean Air', which further emphasised the importance of clean air for healthy lungs. This impactful theme addressed issues such as the significant importance of lung health and the need to increase awareness of lung disease. On par with this initiative, the World Health Organization (WHO) provided an updated version of the outdoor air quality guidelines.

A record-breaking 22,000 delegates from around the world were in full attendance, with >4,200

"The Chairs of the Scientific and Education Councils, together with all of the ERS officers, have prepared an outstanding scientific and educational programme..."

Prof Peter Barnes,
Former ERS President (2013-2014)

accepted abstracts, and >100 exhibitors in a united front showcasing the latest developments within respiratory health and disease. The significant rise in attendance can be attributed to the high standards that ERS continues to strive for. The scientific programme covered a wide range of topics including: asthma, idiopathic pulmonary fibrosis (IPF), chronic obstructive pulmonary disease (COPD), tuberculosis (TB), lung cancer, etc. delivered in stimulating formats such as presentations, symposia, seminars, and workshops.

Commenting on the impressive scientific programme, Prof Peter Barnes, Former ERS President (2013-2014), stressed: "The Chairs of the Scientific and Education Councils, together with all of the ERS officers, have prepared an outstanding scientific and educational programme to address the needs, not only of respiratory health specialists and scientists, but also healthcare professionals and general practitioners."

In addition to air pollution, the next topic of particular interest is TB, for which the WHO launched its eight-point framework which aims to drastically decrease TB incidence on a global scale. Other Congress highlights that piqued the interest among delegates included the development of an electronic nose that can sniff out infant asthma types, research that links paternal smoking to be a potential precursor for childhood-onset asthma, the use of stem cells to alleviate acute respiratory distress syndrome, the connection between asbestos exposure and IPF, and *Aerobika** Oscillating Positive Expiratory Pressure Therapy System, which has the potential to change the future of COPD treatment.

Rising pollution takes toll on European lungs

DECLINING lung health among adult European citizens has been linked to exposure to higher levels of air pollution. Children growing up in areas with higher levels of pollution were also found to have lower levels of lung function as well as a greater risk of developing cough and bronchitis symptoms.

Negative effects of air pollution can particularly affect obese individuals, which is potentially attributed to an increased risk of lung inflammation.

A correlation between air pollution and lung health was investigated in the ESCAPE study, where indicators of traffic in the surrounding area, and exposure levels to pollution measures, such as nitrogen oxides and particulate matter, were modelled. Data on lung function were collected from 7,613 adult participants through spirometry testing spanning 8 different countries including Switzerland, UK, Germany, Italy, Belgium, Spain, and Sweden.

> "The findings of this study demonstrate the importance of educating about clean air and the negative effects of air pollution. Urgent action is needed to tackle air pollution in Europe."
>
> *Prof Peter Barnes, Former President of ERS (2013-2014)*

According to Prof Oliver Eickelberg, Chairman, Comprehensive Pneumology Center, Helmholtz Zentrum München and the Ludwig-Maximilians-University of Munich, Munich, Germany, the air quality in Europe is not safe, even though many people are under the impression that it is.

As reported by the World Health Organization, air pollution accounted for approximately 7 million deaths in 2012, and of these, 3.7 million were linked to poor outdoor air quality. A significant proportion of the population in Europe live in areas with poor air quality that is recognised as having a negative impact on one's overall wellbeing.

"The findings of this study demonstrate the importance of educating about clean air and the negative effects of air pollution. Urgent action is needed to tackle air pollution in Europe," said Prof Peter Barnes, Former President of ERS (2013-2014), Lausanne, Switzerland.

On par with the ESCAPE study is the launch of the Healthy Lungs for Life campaign, which will aim to raise awareness of the importance of healthy lungs and clean air - free from many forms of air pollution.

WHO air quality guidelines reap rewards

MILLIONS have benefitted from improved lung health, thanks to the World Health Organization (WHO) for providing outdoor air quality guidelines.

The key to a healthy human population is clean air, yet pollution threatens the physical wellbeing of populations all over the globe. The WHO estimates that air pollution caused seven million premature deaths in 2012, with the majority being linked to poor outdoor air quality.

Ms Zsuzsanna Jakab, WHO regional director for Europe, said: "Despite progress, 80% of people in the European Union live in cities where levels of air pollution still exceed our recommendations, and citizens in the most polluted cities could add 20 months on average to their life expectancy if the guidelines were followed.

"Health is everybody's business. While we guide the design of effective measures and policies, the health sector must reach out, convincing policy makers for transport, energy, agriculture, urban, and land management to act appropriately, and improve the health and wellbeing of our citizens."

Guidelines helping to assess public health risks of air pollution are essential to the decision-making community. The WHO issued its first set of air quality guidelines in 1987, and these have since been updated in 2000 and 2005; a further revision is to be initiated based on expert reviews of the latest scientific research on the health effects of air pollution, and aiming to provide a solid evidence base that policy makers may use to inform their decisions.

The most recent guidelines cover the four main pollutants of outdoor air, and maximum recommended time periods of exposure are assigned to each – particulate matter, ozone, nitrogen dioxide, and sulphur dioxide – so that countries know what they should be aspiring towards. Additionally, further information on health implications is given to support highly polluted countries in making extensive improvements.

The WHO has recently been awarded the annual European Lung Foundation Award, which recognises the organisation in celebration of its 'breathe clean air' message. Mrs Monica Fletcher, Chair of the European Lung Foundation, Sheffield, UK, commented regarding the award: "We believe that the work of WHO is essential to help us protect the lungs of all citizens and especially those living with chronic lung conditions.

"The WHO guidelines represent a key milestone in the fight for clean air and I would like to offer my congratulations to Zsuzsanna and WHO for their outstanding work."

Global giants step up worldwide tuberculosis cull

ELIMINATION of tuberculosis (TB) in low-incidence countries has been given a much-needed boost through the launch of a new framework by the World Health Organization (WHO) and ERS.

Over 30 countries and territories, in which there are <100 TB cases per million of the population, have signed up to the eight-point framework. This builds on the WHO's post-2015 global TB strategy – to decrease global TB incidence by 90% before 2035.

While TB is most prevalent in low and middle-income countries, it remains a persistent health threat in high-income countries, particularly in the poorest and most vulnerable population sections. Although the disease is preventable and curable, 155,000 people fell ill with TB in low-incidence countries in 2012, leading to 10,000 deaths at an average of 30 TB deaths a day.

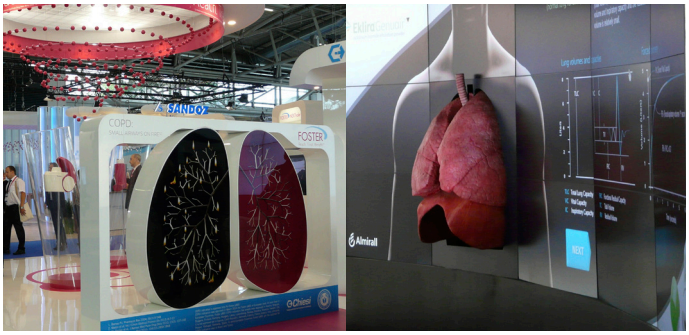
A list of goals aimed at wiping out TB in these countries is outlined in the framework. The 'pre-elimination' phase seeks to have <10 new TB cases per million people by 2035, while the ultimate phase looks to secure the full elimination of TB by 2050.

"These countries recognise the common need to re-energise efforts to eliminate TB as a public health problem and prevent its resurgence. They already have the means to drive down TB cases significantly by 2035 and can serve as global trailblazers," said Dr Mario Raviglione, Director of WHO's Global TB Programme. "As TB rates have fallen in many of these countries, attention to this public health threat has waned and capacity to respond could be weakened. The key is to target smart TB interventions towards the people who need them most."

The spread of TB from high-incidence to low-incidence countries has been catalysed by globalisation and an increase in population movements. Stronger cooperation between countries, as well as a drastic increase in TB prevention and care in high-incidence countries, has been called for in response to this growing international concern.

Prof G.B. Migliori, Secretary General of the ERS, said: "The ultimate goal of international and national public health authorities is the elimination of TB. Although the disease has declined substantially in high-income countries, we must not become complacent.

"Recently, new strains of the disease have emerged that are resistant to the commonly used drugs and we must reinforce our commitment to ending the global tuberculosis epidemic."



DynaPort providing an insight into the life of a patient with COPD

MEASURING physical activity in patients with chronic obstructive pulmonary disease (COPD) has now been made possible through the use of a DynaPort MoveMonitor, developed by McRoberts, The Hague, the Netherlands.

COPD causes around 25,000 deaths a year in the UK, but this could be prevented if lifestyle changes such as physical activity are implemented; however, it can be a difficult challenge in this population. The aim of this device is to help reduce this burden, and recent studies have highlighted its many benefits. It is no wonder, therefore, that it was highlighted as one of the four most innovative products in respiratory care at the ERS Congress this year.

COPD is caused through smoking; the longer you smoke, the more likely you are to develop the condition. While this population is not as active as others, this device can be a useful insight for healthcare providers into the lives of these patients.

The DynaPort has proven its worth within the pulmonary community, being recognised as a valid tool to estimate energy expenditure (EE) related to sedentary physical activities. EE may vary depending on a number of factors including: intensity, duration, the frequency of the activity, body mass, and fitness of the individual.

In order to estimate EE related to sedentary physical activities, the DynaPort is fitted with a tri-axial seismic accelerometer. The device, which weighs only 55 g and is powered by a lithium polymer battery, is to be worn on the lower back by a patient for a period of 7 days, for 24-hours a day.

The day-to-day activities of a patient, such as lying, sitting, standing, locomotion (walking and shuffling), and the transitions between posture and motion, are detected through algorithms from acceleration signals. These data are then recorded by the device and generate automatic numerical and graphical reports, providing data for research as well as patient feedback.

The data generated enable both researchers and clinicians to quantify the daily activity of a patient, allowing them to understand a patient's habitual activity and assess the appropriate respiratory interventions, pulmonary rehabilitation, and the impact of therapeutic interventions such as ambulatory oxygen or new medications. Moreover, these data can help to encourage education and self management.

Based on comparative validation studies by the European Consortium PROactive, funded by the Innovative Medicines Initiative, the DynaPort MoveMonitor is ranked among the best monitors available.

Palliative care: let's talk about it

> "PC needs can be addressed from an early stage of an illness to ensure we are increasing the quality of everyday life for our patients."
>
> *Ms Camilla Mousing, Randers School of Nursing, VIA University College, Randers, Denmark*

HEALTHCARE professionals are being called upon to discuss palliative care (PC) needs for chronic obstructive pulmonary disease (COPD) in more detail.

Linked to end-of-life care, PC focuses on making a patient comfortable and relieving their symptoms, rather than treating the condition. Previous studies brought to attention the barriers that healthcare professionals face in talking about PC; one of the main reasons that professionals avoid conversation is through fear of destroying a patient's hopes for the future.

Yet, according to recent research, where patients were asked about this factor and their perspectives on discussing PC were assessed, patients would, in fact, prefer to discuss disease management.

Researchers conducted semi-structured interviews with 12 COPD patients; data gathered were descriptively analysed. Findings showed that subjects had several worries about the future but felt uncomfortable bringing up the topic of PC themselves because they did not want to burden others with their concerns.

The outcome of the interview analysis was that patients understood COPD as a serious condition, and felt that healthcare professionals should not be afraid to initiate conversations about PC; the patients did not fear that these discussions would destroy their future hopes.

Ms Camilla Mousing, lead author of the study, Lecturer and PhD student, School of Health Sciences, Randers School of Nursing, VIA University College, Randers, Denmark, said: "We have to overcome our fear of talking about this type of care and explain to patients that this does not mean we are giving up on them.

"PC needs can be addressed from an early stage of an illness to ensure we are increasing the quality of everyday life for our patients. These needs can change on a daily basis for each patient and can be very different between patients. We must be flexible in our approach and ensure we know who is responsible for assessing and taking action."

Asbestos associated with idiopathic pulmonary fibrosis

ASBESTOS exposure could be connected to idiopathic pulmonary fibrosis (IPF) cases, potentially paving the way for a revolutionary change in modern treatment strategies.

Those with an established history of asbestos exposure are currently unable to access new IPF treatments. Asbestosis, which shares symptoms with IPF including breathlessness and a special pattern called usual interstitial pneumonitis, is developed by people with a known history of asbestos exposure. However, the main difference between the diseases is whether a patient is aware of their exposure to asbestos.

"In general it is very difficult to tell whether or not somebody has had a significant amount of asbestos exposure because people are poor historians for this and because you cannot go back in time and measure the exact amount of asbestos fibre that was around that they have experienced," said Dr Carl Reynolds, lead researcher, Honorary Clinical Research Fellow, Faculty of Medicine, National Heart & Lung Institute, Imperial College London, London, UK.

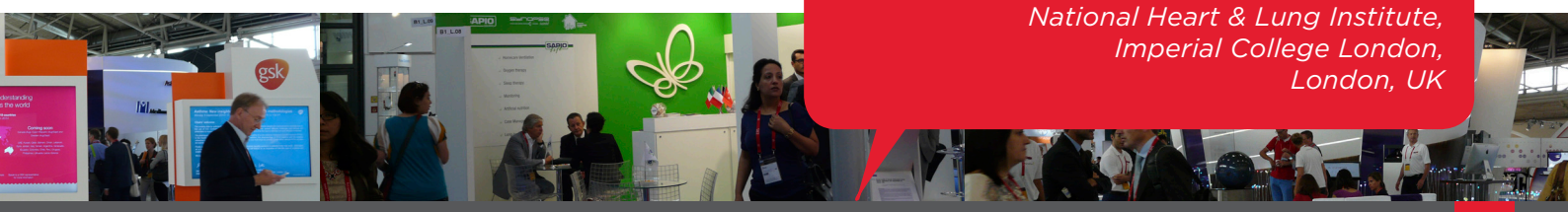
To investigate the hypothesis that IPF is linked to asbestos exposure, mortality rates for IPF, asbestosis, and mesothelioma (the latter two caused entirely and almost entirely by asbestos exposure, respectively) were taken from England and Wales from 1974-2012 using data from the Office for National Statistics. Year-on-year the number of IPF tests increased throughout this period.

Furthermore, there is regional variation in IPF distribution; peak mortality rates were recorded in the North West and South East of England, areas with a history of shipyard work and thus higher potential asbestos exposure. This pattern is not quite as pronounced as the other evaluated asbestos-related diseases, but it does follow the hypothesis.

"More research is needed in this area, particularly as patients known to have asbestos exposure are not currently considered to be candidates for new treatments for IPF and this may be inappropriate," said Dr Reynolds.

"In general it is very difficult to tell whether or not somebody has had a significant amount of asbestos exposure because people are poor historians for this and because you cannot go back in time and measure the exact amount of asbestos fibre that was around that they have experienced."

Dr Carl Reynolds,
National Heart & Lung Institute,
Imperial College London,
London, UK



Smoke drifts from father to baby

The risk of a child developing NAA increased 3-fold if a father started smoking before the age of 15.

FROM 1945-2000, childhood-onset asthma has been shown to increase heavily across the entire two-generational timespan.

Prof Cecile Svanes, Professor, Centre for International Health, Department of Global Public Health and Primary Care, Section for Thoracic Medicine, University of Bergen, Bergen, Norway, stressed the importance of finding the root of the problem of this long-standing issue: "We do not want this increase in all the societies in transition around the world that cannot afford inhaled steroids to treat asthma. It would be a catastrophe."

While it is well-established that a mother's environment plays a key role in the health of offspring, recent studies have emerged indicating that a father's environment before conception could also have a profound effect on a child's health.

Over 20,000 people across Northern Europe took part in the questionnaire-based RHINE study, which took place over a 20-year period. Subjects were asked questions about their smoking habits, including when they started and stopped smoking.

Parents involved in the study were asked to fill out a questionnaire about their offspring, the results revealed that 9% had childhood asthma and 6% had non-allergic childhood asthma (NAA). For NAA, 10% had fathers who smoked only before conception, while 80% had a father who had welded before conception, illustrating the effects of occupational hazards on childhood asthma prevalence.

The risk of a child developing NAA increased 3-fold if a father started smoking before the age of 15. For smoking after the age of 15, the father would have to have smoked for at least 10 years before conception, although there was still a 50% increased risk of NAA in this case.

More studies are required to determine how the effects of smoking and occupational hazards on a father's sperm is transmitted to offspring, although animal models have also shown this pattern.

New nose technology sniffs out infant asthma types

ELECTRONIC nose can detect different sub-groups of asthmatic children, providing an alternative and quicker route to effective diagnosis and treatment for each individual.

The nose may be able to detect eventual asthma sufferers from as early as pre-school ages, and signals an escalating effort to find a cheap and quick method to diagnose an individual with a particular type of asthma. As a result, a more tailored approach to asthma treatment is possible, which may eliminate the one-size-fits-all technique.

Currently the only technology available to detect multiple asthma phenotypes is too expensive for widespread use. However, the aim for Prof Peter J. Sterk, Professor of the Pathophysiology and Phenotyping of Asthma and COPD, Faculty of Medicine, University of Amsterdam, Amsterdam, the Netherlands, and others is to unearth a technique which will be cheap enough to be available in the office of every doctor worldwide.

"I think the time has now come that this is completely turned upside down, that cheap technology, available to the patient in its own or at least in every doctor's office, really cheap technology, disposable technology, will help medicine further," said Prof Sterk.

Different types of asthma may be sub-classified based on the measurement of exhaled breath via the cheap electronic nose technology, which was tested in the pan-European U-BIOPRED project.

The profile of exhaled breath in samples from 106 children with asthma or wheeze were investigated during the study. Of the sample, some were using drugs to treat asthma and some were not, and of the drug sub-group some were allergic to this treatment while others were not. Upon exhaled breath measurement, 180 sensors on the nose construct a biograph of a patient based on particles in the breath called exhaled volatile compounds.

These breath fingerprints, along with the biograph, help to assemble five different clusters of patients which differ in age and asthma symptoms. These clusters can be captured and visualised in the three-dimensional topological analysis, which arranges the clusters into circles; the colour of these circles informs the doctor if the infant is wheezy or asthmatic, and whether the asthma in a patient is severe or mild.

"The electronic nose captures this without knowing the patient's symptoms, and this is just a matter of 2 minutes in the doctor's office," said Prof Sterk.

Stem cells help to fight inflammation in acute respiratory distress syndrome

STEM cells (SCs) may actively help to improve lung function in individuals suffering from acute respiratory distress syndrome (ARDS), new research highlights.

Past investigations have shown that SCs have the ability to reduce lung inflammation and restore some lung function in ARDS; yet, until now, researchers have not been able to explain just how this occurs.

ARDS is a life-threatening condition, one which severely reduces the efficiency of the lungs. It is caused by damage to the capillary wall from either illness or physical injury. The condition is characterised by excessive and dysregulated inflammation, and patients require mechanical ventilation in order to breathe.

Inflammation is normally a means by which the body heals and copes with infection; however, dysregulated inflammation can lead to significant damage - immune cells (macrophages) coordinating the inflammatory response may either suppress the inflammation or drive it.

Researchers sought to investigate whether SCs affected the stimulation of macrophages and promoted the state in which they would suppress inflammation.

Using mice and human bone marrow-derived SCs, the creatures were infected with live bacteria, inducing acute pneumonia and modelling the condition of ARDS. Findings showed that SC treatment led to significant reductions in lung injury and inflammation, improving bacterial clearance. Importantly, mice that had their macrophages artificially removed, lost the protective effects of the SCs given to them.

Results were supported further by experiments using human macrophages in ARDS lung fluid samples; authors have identified numerous proteins that could be responsible for the promotion of this anti-inflammatory state.

This new research is particularly useful, bringing scientists a step closer to understanding the mechanisms and processes that occur within injured lungs, and providing a direction for future patient care for sufferers of ARDS.

Dr Anna Krasnodembskaya, lead study author, Lecturer, School of Medicine, Dentistry and Biomedical Sciences, Queen's University Belfast, Belfast, UK, said of the investigation: "This is the first study to our knowledge that has looked at how SCs can change the functional properties of the macrophages in both humans and a mouse model. The findings highlight the advantages of SC treatment, as they can actively respond to the local micro-environment and exert multiple beneficial effects. We believe that clinical trials are now needed to test whether this can be an effective treatment for people suffering from ARDS."

Exhaled breath: new biomarker for lung cancer

LUNG cancer (LC) can be diagnosed simply by measuring the temperature of exhaled breath. This simple and non-invasive method can potentially revolutionise the way that this cancer is diagnosed, as it could either confirm or reject the presence of LC.

On a global scale, LC is considered the most common cancer, with approximately 1,825,000 new cases diagnosed in 2012. Incidence rates are greatest in North America and smallest in Middle Africa. In Europe, it is the fourth most common cancer, with more than a staggering 410,000 new cases diagnosed in 2012.

According to researchers from the University of Foggia, Foggia, Italy, the pathogenesis of LC stems from both airway inflammation and angiogenesis. Of vital importance is the temperature of exhaled breath, which can be a potential indicator of airway inflammation and increased vascularity. Their study aimed to bridge the link between exhaled breath and potential clinical outcomes of patients with cancers.

> "If we are able to refine a test to diagnose LC by measuring breath temperature, we will improve the diagnostic process by providing patients with a stress-free and simple test that is also cheaper and less intensive for clinicians."
>
> *Prof Giovanna Elisiana Carpagnano, Institute of Respiratory Disease, University of Foggia, Foggia, Italy*

The study included 82 participants who were to be analysed for a full diagnostic test after an X-ray revealed the presence of cancer. A breath thermometer device called an X-Halo was used to measure the temperature of exhaled breaths of the study population. The results revealed that the 40 subjects who had tested positive for cancer also had a comparatively higher breath temperature than those without.

Interestingly, temperature of breath increased with the number of years a person spent smoking, as well as the stage at which their LC had developed. A cut-off value was observed in the measurement of temperature which can identify LC with a high level of accuracy.

"Our results suggest that LC causes an increase in the exhaled temperature. This is a significant finding and could change the way we currently diagnose the disease. If we are able to refine a test to diagnose LC by measuring breath temperature, we will improve the diagnostic process by providing patients with a stress-free and simple test that is also cheaper and less intensive for clinicians," said Prof Giovanna Elisiana Carpagnano, Department of Medical and Surgical Sciences, Institute of Respiratory Disease, University of Foggia.

The mind matters when treating asthma

> "The results of our study can be a key factor in the current debate on how to treat people with severe asthma."
>
> *Dr Andrew Tan, University Hospital Southampton, Southampton, UK*

IMPROVING symptoms of severe asthma patients is helped by psychological input into their treatment and disease management.

Sufferers of severe asthma experience symptoms that are difficult to treat, and current debates focus on the best ways to manage the condition. Yet, while approximately 27% of people with the condition are predicted to encounter psychological problems, this fails to be routinely addressed by healthcare professionals.

However, researchers investigating the effects of time spent with a clinical psychologist in 13 subjects, identified as having psychological illness alongside an admission to hospital with an asthma exacerbation in the last year, suggests that severe asthma symptoms can improve when the mental needs of patients are addressed.

Participants were monitored for admissions to and days in hospital in the 6 months before the psychologist's input, and the 6 months following. Results showed that prior to appointments, the total number of asthma admissions and hospital days was 19 and 159, respectively. Yet after psychological support, these decreased to 10 admissions and 93 days, signalling a 42% drop in hospital days across 6 months.

The study comes after the National Review of Asthma Deaths, 4 months ago, attempted to identify where treatment could be better managed in asthma patients, and found that the majority of those who had died as a result of asthma-related deaths in 2012 had attended emergency departments at least once in their last year of life.

Dr Andrew Tan, University Hospital Southampton, Southampton, UK, commented: "The results of our study can be a key factor in the current debate on how to treat people with severe asthma. We know that a significant proportion of these patients experience psychological issues and these results demonstrate that by tackling these problems, we can also help improve asthma symptoms. This not only helps to improve the quality of life for the patient, it also eases the burden on healthcare systems by reducing the amount of time these patients are in hospital."

Modern innovations in respiratory care

INNOVATIONS in sleep and respiratory care have been showcased by Philips, with the release of a range of products helping healthcare professionals to diagnose, treat, and manage sleep and breathing disorders.

"It is becoming increasingly important for healthcare professionals to have access to comprehensive solutions that enable them to monitor patient progress across the entire continuum of care," said Prof Teofilo Lee Chiong, Chief Medical Liaison, Philips Respironics, Murrysville, Pennsylvania, and Professor of Medicine, School of Medicine, University of Colorado Denver, Denver, Colorado, USA. "Philips understands the complex needs of both patients with sleep and breathing issues and their care providers."

Clinicians find it increasingly difficult to diagnose and manage patients with complex sleep conditions, both efficiently and cost-effectively, in current, changing healthcare settings. In response, Philips is catering to the needs of healthcare professionals with dynamic products that identify, remedy, and manage sleep disordered breathing, as well as increasing patient compliance and adherence to treatments.

A variety of connected products and services, demonstrating the company's commitment to disease management, are available for physicians to experience first-hand. Concerning diagnosis, the new Alice NightOne home sleeping system features an easy-to-use 'smart guide', enabling patients to set up the device confidently themselves; the data display provides physicians accurate information to differentiate between obstructive, central, and positional sleep apnoea.

Additionally, the Omnilab + multi-mode titration system is an enhanced system that reliably monitors sleep, and incorporates nine different therapy modes: more than any other available system.

As one in a range of therapy options for treating obstructive sleep apnoeas and complex breathing disorders, the Philips BiPAP AutoSV Advanced System One device treats sufferers of mixed apnoea, complex sleep apnoea syndrome, or central sleep apnoea with/without periodic breathing.

Philips continues to highlight key respiratory drug delivery, oxygen therapy, and home ventilation innovations, improving the management of chronic respiratory diseases. Philips will conduct a chronic obstructive pulmonary disease exacerbation prevention survey in order to better understand physicians' needs in respiratory medicine.

Food intake timing and carbohydrates hinder tuberculosis treatment

CONSUMING food, particularly meals high in carbohydrates, just before taking tuberculosis (TB) medication can hinder the effectiveness of treatment; this news comes as a warning to TB patients across Europe.

20 subjects who were in the early phases of TB treatment for the first time enrolled in a small study; they were given the usual cocktail of isoniazid, rifampicin, pyrazinamide, and ethambutol. On the first day, the drugs were administered by injection, and on the second and third, they were given orally to individuals who were either fasting or consuming a high-carbohydrate meal.

"In the first weeks of TB treatment, the number of bacterial load is high and therefore the inadequate level of drugs can let through the resistance of the TB bacilli, especially to isoniazid and pyrazinamide, which are the most powerful TB drugs for these first weeks of treatment," said Dr Antonia M. Iswari Saktiawati, Centre for Tropical Medicine-Research Collaboration Unit, Faculty of Medicine, Gadjah Mada University, Yogyakarta, Indonesia, and PhD student, Medical Science Department, University of Groningen, Groningen, the Netherlands.

Researchers collected blood samples from each participant which were further analysed using a technique called liquid chromatography tandem-mass spectrometry; this separated the sample and gave information about the chemicals present within it.

Using this technique, information was obtained in relation to the drug's concentration levels and the fraction of the unchanged drug that reached circulation.

Blood samples were taken again from the same individuals in the same environment, but only the food intake was altered. It was observed that when drugs were taken with a high-carbohydrate meal, the three drugs (i.e. isoniazid, rifampicin, and pyrazinamide) had a relatively lower concentration in the blood, compared to when they were given in a fasting state. It was then proposed, based on these observations, that the TB medication became less effective if a high-carbohydrate meal was consumed before taking the drugs.

"As the research was conducted in the same people and the same environment, the only variable was the meals and we therefore know that food can have an impact on the concentration of the drugs in the blood. The findings may have significant implications for clinical practice as we must ensure that patients are taking the drugs in the correct way to be as effective as possible," said Dr Saktiawati.

"As the research was conducted in the same people and the same environment, the only variable was the meals and we therefore know that food can have an impact on the concentration of the drugs in the blood."

Dr Antonia M. Iswari Saktiawati, Centre for Tropical Medicine-Research Collaboration Unit, Gadjah Mada University, Yogyakarta, Indonesia

Aerobika coughs up solution for COPD

> "The results from this study provide compelling evidence that patients suffering from COPD or bronchiectasis now have a safe and easy-to-use method to address the unmet need of mucus clearance and improve their quality of life."
>
> *Dr Jason Suggett, Group Director, Science and Technology, Trudell Medical International, London, Canada*

250 MILLION chronic obstructive pulmonary disease (COPD) sufferers worldwide could feel the benefits of the award-winning *Aerobika** Oscillating Positive Expiratory Pressure (OPEP) Therapy System, a potential spearhead for effective future COPD treatment.

Cough and sputum production, frequent in COPD and bronchiectasis sufferers, is associated with premature death and increased occurrence of exacerbations, hospitalisations, and death. OPEP aims to facilitate mucus and sputum clearance; however, up until now there has been insufficient clinical evidence of its effectiveness; COPD was projected to cost the USA alone approximately $50 billion, with hospitalisations accounting for the majority of these costs.

50% of COPD hospital admissions are linked to bacterial infections - this prevalence increases in uncleared mucus - while patients with COPD and mucus are more likely to die from pulmonary infections.

Developed by Trudell Medical International (TMI), London, Ontario, Canada, the *Aerobika** OPEP Therapy System – currently available in Canada, the USA, and several other countries - is a drug-free, handheld device that assists COPD sufferers to breathe and live more comfortably by addressing the unmet need of mucus clearance. When a patient exhales through the device, intermittent resistance simultaneously creates positive pressure and oscillations, mobilising and aiding mucociliary clearance to the upper airways, where it may be coughed out.

14 COPD and 14 bronchiectasis sufferers were randomised to perform OPEP four times daily across 3 weeks in a cross-over controlled study, completed at the Robarts Research Institute, University of Western Ontario, London, Ontario, Canada. Drastic improvements in clinical and patient recorded outcomes were seen, including easier mucus clearance, decreased cough frequency and breathlessness, and increased exercise tolerance.

"The results from this study provide compelling evidence that patients suffering from COPD or bronchiectasis now have a safe and easy-to-use method to address the unmet need of mucus clearance and improve their quality of life," said Dr Jason Suggett, Group Director, Science and Technology, TMI. "We are also excited about the future possibility of looking at the longer term impact on patient outcomes and healthcare system efficiencies."

ERS ANNUAL CONGRESS 2014

ICM-MESSE MÜNCHEN
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ERS AWARDS 2014

PRESIDENTIAL AWARD

Prof Robert A. Stockley, UK

CONGRESS CHAIR

Prof Werner Seeger, Germany

ELF AWARD 2014

Ms Zsuzsanna Jakab, Regional Director for WHO Europe, Denmark

LIFETIME ACHIEVEMENT AWARDS

ERS Award For Lifetime Achievement In Pulmonary Arterial Hypertension

Prof Marius M. Hoeper, Germany

Assembly Lifetime Achievement Award

Prof Andrew Bush, UK

Assembly Lifetime Achievement Award

Prof Elisabeth Quoix, France

ERS Research Award on Idiopathic Pulmonary Fibrosis

Dr Melanie Königshoff, Germany

Cell-specific effects of canonical and non-canonical Wnt signalling in chronic lung disease.

ERS Award for Rare Pulmonary Disease

Prof Matthias Griese, Germany

Orphan's unite: chILD better together – European Management Platform Childhood Interstitial Lung Disease.

ERS Romain Pauwels Research Award

Prof Christopher Brightling, UK

The mechanisms that underpin airways disease, biomarkers of disease, the translation of laboratory-identified targets to clinical trials, the inclusion of these findings into evidence-based guidelines, and the imple-mentation of these guide-lines into clinical practice.

Educational Award

Prof Paolo Palange, Italy

Former Chair of ERS Education, he is the recipient of this year's Educational Award in recognition of his dedication to furthering educational opportunities for respiratory professionals.

THERE'S MORE TO IgE – LET'S TALK SEVERE ASTHMA

Summary of Presentations from a Novartis-Supported Satellite Symposium, held at the 24th ERS Congress, Munich, Germany, on 7th September 2014

Chairperson

Roland Buhl[1]

Speakers

Gary Anderson,[2] William Busse,[3] Jan Lötvall,[4] David Price[5]

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4. University of Gothenburg, Gothenburg, Sweden
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Disclosure: Prof Buhl has provided lecturing and consulting activities for Aerocrine, AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Grifols, Novartis, Roche, Takeda, and Teva. He receives research support (Mainz University) from Boehringer Ingelheim, GSK, Novartis, and Roche. Prof Anderson has received compensation from Boehringer Ingelheim, AstraZeneca, MundiPharma, Novartis, Menarini, Takeda, and GSK for participating in meetings and advisory boards. Prof Busse is a consultant for Novartis, GSK, Genentech, and Roche. He serves on data monitoring boards and study oversight committees for Boston Scientific, Genentech, and ICON, and has research/organisational interests in AAAAI, ATS, AAP, ACAAI, AAI, ACP, CIM, NHLBI, and NIAID. Prof Lötvall has relationships with Abdilbrahim, Aerovant, AstraZeneca, GSK, Novartis, MSD, and UCB. Prof Price is a board member for Aerocrine, Almirall, Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, Meda, Mundipharma, Napp, Novartis, and Teva. He provides consultancy for Almirall, Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Meda, Mundipharma, Napp, Novartis, Pfizer, and Teva. He has grants and grants pending from the UK National Health Service, British Lung Foundation, Aerocrine, AstraZeneca, Boehringer Ingelheim, Chiesi, Eli Lilly, GSK, Meda, Merck, Mundipharma, Novartis, Orion, Pfizer, Respiratory Effectiveness Group, Takeda, Teva, and Zentiva. He has received payments for lectures/speaking/manuscripts/educational materials from Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, GSK, Kyorin, Meda, Merck, Mundipharma, Novartis, Pfizer, SkyePharma, Takeda, and Teva. He owns shares in AKL Ltd., which produces phytopharmaceuticals and owns 80% of Research in Real Life Ltd. and its subsidiary social enterprise, Optimum Patient Care. He has unrestricted funding for investigator-initiated studies from Aerocrine, AKL Ltd., Almirall, Boehringer Ingelheim, Chiesi, Meda, Mundipharma, Napp, Novartis, Orion, Takeda, Teva, and Zentiva.
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MEETING SUMMARY

The meeting discussed the current understanding of the role of immunoglobulin E (IgE) in asthma, and anti-IgE strategies in the treatment of severe asthma. Prof Gary Anderson provided an overview of the integral role of IgE in the inflammatory pathways involved in the pathogenesis of severe asthma and the development of omalizumab (Xolair®), an anti-IgE therapy. Prof William Busse presented some of the clinical findings on the use of omalizumab for virus-provoked asthma. Prof Jan Lötvall discussed how phenotyping could improve the development of patient-targeted treatment strategies in asthma. Finally, Prof David Price discussed how changes to the clinical management of patients with severe asthma could improve patient outcomes.

Chair's Opening Comments

Professor Roland Buhl

There is a widespread and growing prevalence of asthma, with 300 million cases worldwide.[1] In Europe, asthma causes 15,000 deaths[2] and accounts for 5 million disability-adjusted life-years annually.[1] One study revealed that patients who continue to experience asthma symptoms despite using inhaled corticosteroids (ICS), as well as long-acting β_2-agonists (LABA), can achieve guideline-defined control of asthma by increasing ('stepping-up') their use of these medications.[3] However, this study also revealed that a significant number of asthma patients can remain uncontrolled despite very high doses of ICSs and LABAs.

Severe asthma has been defined by an ERS/American Thoracic Society-led task force[4] as a disease that requires treatment with high-dose ICSs plus a second controller and/or systemic corticosteroids, or a disease that remains uncontrolled despite this therapy. Severe asthma should be distinguished from difficult-to-treat asthma, which includes patients with poor treatment compliance and/or persistent exposure to environmental allergens. Using this definition, European prevalence estimates of severe asthma range between 5-10%.[4]

The 2014 Global Initiative for Asthma guidelines[1] recommend increasingly high dosages of ICSs and LABAs when asthma symptoms persist, until they are brought under control. If medium-to-high doses of these fail, anti-IgE treatments are suggested in those with a history of allergies.[1] Analysis of The German Severe Asthma Registry[5] found that >50% of patients with severe asthma had a positive skin-prick test (SPT) against common allergens and asthma symptoms that correlate with allergen exposure. A further 15% also have a positive SPT, but without clear correlation between symptoms and allergen exposure.[6] For these reasons, it seems logical to discuss treatment strategies that target severe allergic asthma, thereby reducing symptoms and improving quality of life (QoL) in these patients.[7]

IgE: The Whole Story

Professor Gary Anderson

There is an established link between IgE levels and the risk of asthma.[8] Our understanding of this link has previously assumed that T-helper Type 2 (Th2) cells interact with B lymphocytes to induce IgE production. An elevated level of IgE was then assumed to promote inflammation when sensitised mast cells degranulate and thereby cause changes in lung function and increase asthma symptoms. Omalizumab was therefore developed to reduce the allergic response by blocking the high-affinity IgE receptor (FcεRIβ) present on mast cells. However, current understanding of asthma is much more sophisticated, and recognises that many different endotypes exist that are defined by distinct pathological mechanisms.[9]

While the mode of action of omalizumab – to bind and neutralise IgE without triggering high affinity IgE receptors – is understood in exact molecular detail, its efficacy in different disease endotypes is less clear. However, investigation of the impact of omalizumab on the cellular and molecular markers that contribute to the immune response has provided new insights. For example, analysis of airway mucosa of individuals with asthma and taking omalizumab revealed effective removal of IgE from both high and low-affinity IgE receptors,[10] and this was, in turn, associated with a marked reduction in the expression of the high-affinity IgE receptor. Decreased receptor density after omalizumab treatment has also been shown in other studies,[11,12] and its therapeutic benefit may derive from an overall reduction in sensitivity to IgE.

When the immune response is reduced, the propensity for exacerbations should also decrease. Eosinophils are key cells within the immune system that may determine the risk of exacerbations in asthma. Furthermore, it has been established that ICS treatment titrated entirely by eosinophil sputum levels, rather than asthma control, can reduce the risk of exacerbations.[13] A second known risk for exacerbations is reduced Type 1 anti-viral interferon levels. A key source of Type 1 interferons are the plasmacytoid dendritic cells (pDCs). If the high-affinity IgE receptor located on these cells is bound by IgE, there is a resulting decreased production of protective Type 1 interferons. Omalizumab both reduces eosinophil levels[10,14] and downregulates the high affinity receptor on pDCs,[15] which may account for the clinically proven ability of omalizumab to reduce the forward risk of exacerbations.[16-22]

In summary, IgE is intimately related to asthma risk, working through multiple pathways. Omalizumab profoundly reduces blood IgE levels, reducing the sensitivity of the system and therefore the T2

immune response. The risk of exacerbations might also be reduced with omalizumab by decreasing eosinophil levels and increasing production of Type 1 anti-viral interferons.

Clinical Benefits of IgE Blockade

Professor William Busse

Viral respiratory infections, particularly the common cold virus, rhinovirus, are a major cause of asthma exacerbations. Not every patient with asthma experiences an exacerbation with a respiratory infection. Conversely, not every respiratory infection leads to an asthma exacerbation, even in high-risk patients. A number of risk factors have been identified, including allergic sensitisation. This association points to IgE as also being involved in exacerbations. Clinical research has also indicated the importance of IgE-sensitisation as a risk for an asthma exacerbation with a rhinovirus respiratory infection. A large study conducted in Costa Rica by the University of Virginia[23] recruited three groups: children with asthma and exacerbation, children with asthma but without exacerbation, and normal controls. They found that the level of IgE to house dust mite was a risk factor for wheezing. However, the risk for wheezing was markedly enhanced by the presence of a rhinovirus respiratory infection, suggesting a link between wheezing with a rhinovirus infection and the IgE-allergic sensitisation process.

The link between asthma and altered anti-viral responses has been investigated by Sebastian Johnston and colleagues at Imperial College, London, UK.[24] They obtained bronchial epithelial cells from children with asthma and normal subjects. Bronchial epithelial cells from asthmatic patients generated less interferon-β and interferon-λ production in response to rhinovirus. This suggests that the anti-viral response to rhinovirus may be impaired in asthma. Previous work has also shown that pDCs from patients with asthma have a diminished interferon response (i.e. interferon-α) when incubated with influenza or rhinovirus.[25]

It is also known that asthma exacerbations have a seasonal variation, with a marked increase in hospitalisations occurring in September, when children return to school.[26] At this time of year, as well as children returning to school, and therefore increasing their proximity to one another, it is also a time of increased environmental allergen exposure. This study raises the possibility that the likelihood of an asthma exacerbation is enhanced when respiratory infections occur in the presence of heightened allergic symptoms.

In a randomised trial comparing omalizumab and guideline-directed care, omalizumab reduced exacerbations and virtually eliminated the exacerbations of asthma during the fall.[27] Following these results, the PROSE study[28] was designed to determine whether omalizumab might be beneficial if used preventatively, immediately prior to children returning to school. PROSE has recently been completed, and the results are being reviewed.

Does Phenotyping Matter?

Professor Jan Lötvall

The term 'phenotype' can be defined as the 'observable, physical characteristics' of an organism that enables it to be classified within a group, and distinguished from others. Sally Wenzel[29] brought forward the idea that we should distinguish between phenotypes of asthma patients in order to be able to better understand their individual disease-related characteristics. She described three phenotype characteristics that should be considered, including 'clinical physiology', 'environmental triggers', and 'pathology/inflammation'. Since then, five different phenotypic clusters have been described in several studies, which are based on age of onset and severity of symptoms, lung function, and medication use.[30] However, there is much overlap between these phenotypes, leading us to propose a classification system based on 'endotypes' of disease. This aims to understand distinct molecular mechanisms of subsets of disease.[31] From the available data, these endotypes may be separated either on Th2-associated or Th2-independent processes.

Anti-IgE therapy has historically been applied to patients with an allergic phenotype, but these may not fully represent the severe asthma group. Therefore, while omalizumab should be prescribed in individuals with high IgE levels or a positive SPT, phenotyping will become ever more important for the development of future mechanism-targeted therapies.

Improving the Severe Asthma-Patient Journey

Professor David Price

The goals for the treatment of severe asthma are to prevent death, minimise symptoms, and reduce exacerbations. A UK-based review of asthma-related deaths revealed that these remain disappointingly high.[32] 43% of people who had died were managed in secondary or tertiary care during the 12 months prior to their death, and at least 21% had been seen at A&E in the previous year, suggesting that opportunities to intervene had been missed, and patients are not getting the appropriate care even when the warning signs are present. In addition, many patients remain symptomatic and have frequent exacerbations in spite of high-dose combination therapy.

For patients with severe asthma, it is recognised that anti-IgE treatment should be the preferred option, rather than long-term use of oral steroids. High-dose ICS and oral steroids can be lifesaving, but there is a potential for side-effects to arise when taken for prolonged periods. For example, there is increasing evidence of metabolic side-effects of higher dose ICS and frequent oral steroid use.[1] Therefore, a further goal in the management of severe asthma should be to reduce the use of oral steroids and possibly high-dose ICS. To achieve this, we need to communicate better with patients in order to get a more accurate representation of asthma control, and to use better decision-making processes. For example, before stepping-up a patient's therapy, the International Primary Care Respiratory Group[33] recommend considering other options, such as checking that the patient is not being exposed to avoidable external allergens in their home.

An evaluation of the real-world effectiveness of omalizumab was recently published.[34] Patients using omalizumab achieved a reduction in exacerbations that increased over time so that, at 24 months, at least a 67% reduction was achieved. Long-term improvements in QoL were also observed. Furthermore, oral corticosteroid use was reduced.

There are still hurdles to overcome in improving the care of patients with severe asthma. For instance, many patients who are potentially eligible for omalizumab are being referred to centres specialising in severe asthma. It is possible that patients are not being assessed appropriately because their asthma is controlled with frequent use of rescue oral corticosteroids. It should perhaps be recommended that people using two or more courses of steroids in a year should be referred for further assessment so that it can be determined whether omalizumab is an appropriate option. If we can address these issues of referral, patient journeys can be altered and outcomes can improve.

Chair Summary

Professor Roland Buhl

In summary, Prof Roland Buhl made clear that IgE has a central role in severe and allergic asthma, but maybe also in the non-allergic phenotype. He suggested that clinicians should look more carefully at patients with asthma so that anti-IgE therapy is used more, when appropriate. Furthermore, he further suggests that we should move on to evaluate the role that anti-IgE can play in other diseases, such as urticaria, a disease that is totally unrelated to the allergic phenotype, and yet anti-IgE therapy seems to work very well.

Panel Discussion

In considering whether non-allergic asthmatics would benefit from anti-IgE therapy, Prof Lötvall expressed the view that testing for allergies is imperfect due to fluctuating environmental allergen levels, so the more important consideration should be whether or not they respond to anti-IgE therapy. Prof Busse pointed out that the best results of anti-IgE are achieved in those with diagnosed allergies. Prof Price proposed that any patient with problematic asthma should be tested for allergies. He also later indicated that patients with raised eosinophils, but without allergy, might respond to anti-IgE therapy. Another candidate patient group – those with elevated exhaled nitric oxide – was suggested by Prof Busse.

Responding to a question regarding the role of neutrophils in asthma, and whether they should be targeted by treatment, Prof Anderson suggested that while there is a lot of evidence suggesting that reducing eosinophils can improve asthma symptoms, it is less clear that targeting neutrophils would be beneficial.

In a discussion around the specific use of medication for different asthma phenotypes, Prof Lötvall pointed out that certain groups of asthma patients do not respond well to ICSs, but are still offered these in combination with other medications. It is possible that this contributes to an overuse of ICS. However, those with significant disease respond very clearly to ICSs, and we do not have long-term studies that can guide the specific treatment of patients with different phenotypes.

Asked how to best differentiate between severe asthma and chronic obstructive pulmonary disease, Prof Price pointed out that there is a validated questionnaire capable of differentiating between the two conditions. The most important features of the questionnaire were related to evidence of allergies and duration of disease.

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COPD PATIENTS' NEEDS AND CURRENT TREATMENT OPTIONS

Summary of Presentations from a Novartis-Supported Satellite Symposium, held at the 24th ERS Congress, Munich, Germany, on 8th September 2014

Chairperson

Bartolome Celli[1]

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MEETING SUMMARY

The objective of this meeting was to review the complexities surrounding the management and treatment options for different populations of chronic obstructive pulmonary disease (COPD) patients. Bartolome Celli chaired the symposium and outlined some of the current challenges for COPD management. Donald Tashkin discussed clinical assessment of the newly-diagnosed COPD patient, before moving on to review the initial pharmacotherapy options that are available, specifically the long-acting beta or muscarinic agonists. Claus Vogelmeier presented the options for COPD patients who remain symptomatic despite initial treatment, using data from clinical trials such as SPARK to compare different treatment approaches, and Jadwiga Wedzicha focused on higher-risk patients, presenting pertinent data from studies on patients with increased rates of COPD exacerbation. Finally, Bartolome Celli summarised the meeting and provided his expert insight on classifying COPD patients into phenotypic groups.

Welcome and Introduction

Professor Bartolome Celli

In terms of global disease burden, chronic obstructive pulmonary disease (COPD) is associated with 3,659,000 disability-adjusted life years, secondary only to ischaemic heart disease. COPD is also the cause of 154,000 deaths annually, and of 1,913,000 years of life lost.[1] The scale of the challenges within the COPD field is reflected by the active research interest in the field. Over the past 40 years there has been a noted increased interest in COPD with much investigative research and numerous associated publications being produced.

One important current issue that remains within the field is the level of cigarette smoking. Although this is a global issue of epidemic proportions, effective steps can be taken to reduce the proportion of people smoking. This was shown in New York City, where action from advocacy groups and education initiatives has resulted in the percentage of individuals who smoke dropping from an average of 22% in the 1990s to 14% in 2010. This action included tax increases on a local, state, and federal level, free patch programmes, smoke-free workplaces, and media campaigns.[2] Death resulting from smoking and COPD is, however, a problem across the world, and it is important to remember that COPD is not just related to lung disease and airflow; body-mass index, airflow obstruction, dyspnoea, and exercise capacity all contribute to risk of death.[3]

Since COPD is a multi-dimensional disease, the GOLD (Global initiative for chronic Obstructive Lung Disease) assessment tool[4] provides an easy-to-interpret classification system. This assessment tool takes into account the severity of airflow obstruction, symptoms, and exacerbations in order to provide an A/B/C/D classification of disease severity.[4] GOLD shows that in approaching COPD, a healthy lifestyle, smoking cessation, and environmental control are important, exercise and rehabilitation should be performed, and oxygen therapy should be administered.

A pulmonologist has multiple factors to consider when treating a patient with COPD, and has several treatment options and pathways available. The most appropriate therapeutic approach can differ depending on whether the patient is newly diagnosed, is still exhibiting symptoms despite monotherapy or even dual combination therapy, or if the patient is in a high-risk group.

Treating the Newly Diagnosed COPD Patient

Professor Donald Tashkin

It is important to note that newly diagnosed COPD patients may, in fact, have any level of severity of COPD, and therefore should have their level of severity assessed, ideally through a system such as GOLD since it provides a useful guide for initiating pharmacotherapy. In terms of the proportions of patients with mild-to-moderate disease, a study of the UK General Practice Research database classified patients according to the GOLD spirometric grade at time of diagnosis, and found that nearly 50% of patients were at GOLD Grade 2.[5]

An important challenge in COPD is under-diagnosis. Many physicians often rely on symptoms in order to make a diagnosis due to a lack of spirometers in their practice. While symptoms remain an important factor in the diagnostic process, the PLATINO study has evidenced that symptoms alone are insufficient to establish an accurate diagnosis; patients exhibiting shortness of breath, wheezing, cough, and phlegm were very infrequently diagnosed with COPD when spirometry was performed, highlighting the importance of this technique.[6]

Evidencing the challenge of under-diagnosis, it is estimated that COPD is undetected in ~50% of cases,[7] and in addition, COPD is misdiagnosed as asthma in ~23% of cases.[6] These factors mean that by the time a correct diagnosis has been made, up to half of the patient's lung function may have been lost[8] and the opportunity to impact the rate of progression by treating early has been missed. The loss of lung function is accelerated during the early stages of COPD, which provides an opportunity to intervene early and modify disease progression.[9] Early intervention through smoking cessation has been shown to significantly reduce both lung function decline and all-cause mortality in patients with mild-to-moderate airflow limitation,[10] further supporting the need for early intervention.

Once a correct diagnosis has been made, and lifestyle interventions have been considered, therapeutic approaches are important in

the management of COPD. In terms of pharmacotherapy, patients in GOLD category B should be treated with the long-acting beta agonists (LABAs) or long-acting muscarinic antagonists (LAMAs; also known as long-acting anticholinergics), which are bronchodilators that relax the muscles in the airways, decreasing resistance and improving FEV_1.[4,11,12] The 2014 GOLD guidelines recommend the LABAs formoterol, indacaterol, and salmeterol, and the LAMAs aclidinium bromide, glycopyrronium bromide, and tiotropium for inhalation. While there are few head-to-head studies of these drugs, indacaterol and tiotropium have been shown to significantly improve FEV_1 when compared to placebo.[13,14]

There have been several trials examining the effect of bronchodilators on patient outcomes. The UPLIFT trial demonstrated marked improvement in FEV_1 over 4 years in maintenance-naïve patients treated with tiotropium, showing that early intervention had a desirable outcome.[15] Similar improvements were also seen with the LAMA glycopyrronium in the GLOW1 and GLOW2 (Figure 1) trials.[15,16] Data from the INTENSITY trial show that LABA or LAMA monotherapy can improve patient-reported outcomes, which are important goals for COPD management.[17] These therapies improve exercise tolerance, health-related quality of life (QoL), reduce mortality and exacerbations, and also slow disease progression. A LABA/LAMA combination also presents a potential option for improving lung function and health status in maintenance-naïve patients; however, it is unclear which patients would most benefit from starting treatment on this combination compared to monotherapy.

Early treatment is important not only because this causes a symptomatic improvement in the QoL of patients, but it also provides an opportunity to slow the accelerated rate of the decline in lung function that is greatest in the early stages of COPD.

- Improvements in FEV_1 $AUC_{0\text{-}4h}$ were statistically significant with glycopyrronium vs placebo and tiotropium at Day 1 and Week 26, and comparable to tiotropium at Weeks 12 and 52

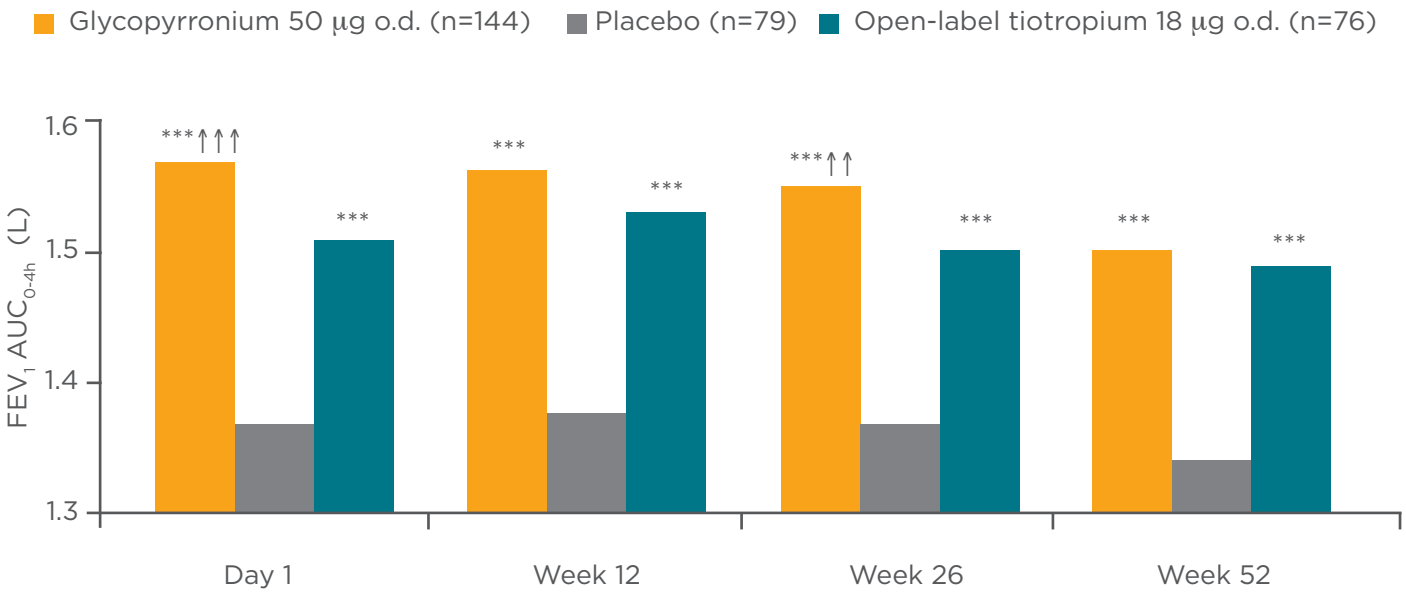


Figure 1: Glycopyrronium and tiotropium significantly improved FEV_1 versus placebo and tiotropium in the GLOW2 trial.

*Based on FEV_1, $AUC_{0\text{-}4h}$ following dosing between 08:00 and 11:00.

***p<0.001, versus placebo;↑↑↑p<0.001, ↑↑p<0.01; glycopyrronium versus open-label tiotropium.

Data are least-squares mean from subset of patients who underwent serial spirometry.

FEV_1: forced expiratory volume in 1 second; AUC: area under the curve; o.d.: once daily.

Adapted from Kerwin E et al.[16]

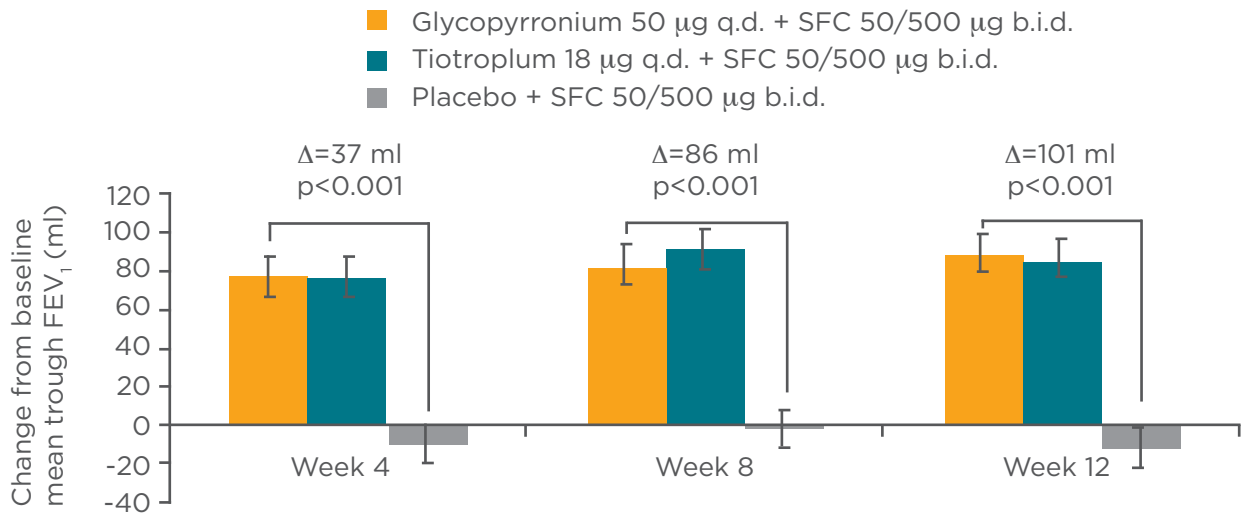


Figure 2: The addition of a LAMA to the LABA/ICS combination improves FEV_1 compared to placebo in the GLISTEN trial.

The primary objective of the study was met (non-inferiority of glycopyrronium 50 µg q.d. versus tiotropium 18 µg for trough FEV_1 after 12 weeks).

Data are least-squares mean±SE.

LAMA: long-acting muscarinic antagonists; LABA: long-acting beta agonists; ICS: inhaled corticosteroid; FEV_1: forced expiratory volume in 1 second; b.i.d.: bis in die (twice a day); SFC: salmeterol/fluticasone propionate; q.d.: quaque die (once daily); SE: standard error.

Adapted from Frith P et al.[34]

Options for COPD Patients who Remain Symptomatic Despite Treatment

Professor Claus Vogelmeier

Considering therapeutic options for those patients who remain symptomatic despite treatment, a patient in GOLD category D, with FEV_1 of 20% and severe emphysema, could potentially be given a LABA/LAMA combination, an inhaled corticosteroid (ICS)/LABA combination, or even an ICS/LABA/LAMA triple combination. LABA/LAMA combinations are suggested for treatment since they have distinct mechanisms of action, and target both the peripheral and central airways.[18]

There is clinical evidence supporting the LABA/LAMA combination, such as the SPARK trial[19] which included very ill patients who had severe or very severe disease and a history of at least one exacerbation; patients receiving QVA149 (indacaterol + glycopyrronium) had consistent and significant improvements in QoL over the 64-week study when compared to glycopyrronium or tiotropium alone. The BLAZE trial,[20] which reported patient outcomes, used a three-period cross-over design. Patients receiving QVA149 had significantly improved transition dyspnoea index (TDI) scores compared to both placebo and tiotropium (0.88 versus -0.49 and 0.39).[20] In terms of head-to-head comparisons of other LABA + LAMA, the QUANTIFY study[21] showed that QVA149 was superior to tiotropium + formoterol for the clinically-relevant endpoint of percentage TDI responders.

There are various choices to make when initiating treatment, and the choice to give monotherapy or combination therapy depends on a number of factors, including whether the patient is newly diagnosed, therapy naïve, or is symptomatic and has exacerbations. A combination of LABA with an anti-inflammatory such as an ICS is more effective than the individual drugs;[22-29] however, no combination treatment has been shown to have a mortality benefit.[22] A problem with ICS treatment, however, is the side-effect profile, the most relevant being the risk of developing pneumonia.[30,31] When considering whether to treat with an ICS, the correct patient type must therefore be selected. The ILLUMINATE trial[32] made it clear that an ICS/LABA combination does not make therapeutic sense for patients with no exacerbation history; patients receiving the LABA/LAMA combination QVA149 had improved TDI scores at both Week

12 and 26 versus the ICS/LABA combination of salmeterol and fluticasone (treatment differences: 0.59 and 0.76). However, despite recommendations, more than one-third of patients in GOLD groups A and B are receiving ICS.[33]

Patients on dual combination therapy showing a continued lack of disease control may require the addition of further medication in order to improve outcomes. The GLISTEN trial (Figure 2) examined the effects of glycopyrronium, tiotropium, or placebo all in combination with salmeterol + fluticasone over 12 weeks. The addition of either LAMA to LABA/ICS improved FEV_1 and QoL compared to placebo, demonstrating that patients who are symptomatic on ICS/LABA may benefit from the addition of a LAMA such as glycopyrronium or tiotropium.[34] A systematic review of four trials determined that ICS withdrawal did not result in an increase in exacerbations.[35] The recently published large WISDOM trial also demonstrated that removing ICS from patients on triple therapy did not lead to significant increases in exacerbation rate, regardless of patient subgroup.[36]

Maintenance therapy with a LABA or LAMA may improve symptoms, but if symptoms persist there are a number of options to consider. A choice must be made whether to treat with a LABA/LAMA or, if the patient has frequent exacerbations, LABA/ICS combination, or with triple therapy. These options depend on the status of the patient and their level of exacerbation risk.

Managing Higher Risk COPD Patients

Professor Jadwiga Wedzicha

The real value of GOLD is that it helps to understand risk and also informs on how to prevent it. Exacerbation risk is complex, and comorbidities are intertwined with this risk; patients who have one exacerbation per year may have heart failure or other issues that increase their risk. Patients in GOLD group B have been shown to have poorer survival rate than those in group C.[37] Overall, 22% of patients with moderate disease (GOLD Stage 2) have two or more exacerbations per year, and since approximately 70% of COPD is in Stage 2, this results in a large amount of morbidity due to exacerbation.[38]

COPD exacerbations can be triggered by bacteria, viruses, and pollutants, resulting in inflamed airways and leading to a number of effects, including: systemic inflammation, bronchoconstriction, oedema and mucous, expiratory flow limitation, and dynamic hyperinflation.[39] Most exacerbations improve in 7–10 days but some persist, and approximately 25% of exacerbations do not recover to a normal state after 5 weeks;[40] this may be due to the persistence over hyperinflation post-exacerbation. More persistent exacerbations have been observed in patients with airway infections,[41] and hospitalisation for COPD is associated with a significant risk of death.[42]

The INSPIRE study showed that exacerbation rates were similar in patients treated with tiotropium or salmeterol + fluticasone.[43] A study that followed on from this was SPARK,[19] which investigated exacerbations in patients treated with QVA149 (indacaterol + glycopyrronium), glycopyrronium alone, or open-label tiotropium alone. All patients had at least one exacerbation in the previous year, and their mean FEV_1 was 37.2% predicted. QVA149 significantly improved mean trough FEV_1 compared to the other two groups over the course of the 64-week study, reduced moderate and severe COPD exacerbations by 12% versus glycopyrronium (primary endpoint; p=0.038) and 10% versus open-label tiotropium (secondary endpoint; p=0.096) (Figure 3), and reduced the annualised rate of total and mild exacerbations. This reduction in rates was associated with improvements in health status over the course of the study. Patients receiving QVA149 self-reported changes from baseline of -0.37 and -0.44 in daily symptoms scores ($p<0.01$) and of -0.09 and -0.13 in dyspnoea scores ($p\leq0.0001$) versus glycopyrronium or tiotropium alone. Daily rescue medication usage was also reduced (-0.81 and -0.76 puffs per day for the two comparisons; both $p<0.001$).[19]

The LANTERN trial, comparing QVA149 against salmeterol + fluticasone in the broader COPD population, included patients with post-bronchodilator FEV_1 of 30–80% predicted and a history of one or more exacerbations. Dual bronchodilation was more effective at improving lung function than ICS/LABA, and reduced the time to first moderate or severe COPD exacerbations by 35% over 26 weeks of treatment (Figure 4; HR 0.65; p=0.028). Importantly, there were slightly fewer adverse events in patients treated with QVA149, but overall the regimens were similar. There was a reduction in incidence of

pneumonia in QVA149-treated patients compared to those on the ICS/LABA combination.[44] The FLAME study[45] is currently ongoing and is investigating QVA149 versus salmeterol/fluticasone in patients with a history of moderate-to-severe exacerbations.

Exacerbations are associated with increases in symptoms and comorbid events, with prior exacerbation being a major risk for future exacerbations. High-risk patients benefit from dual bronchodilation with QVA149, which is an effective therapy shown to both improve lung function and reduce exacerbations.

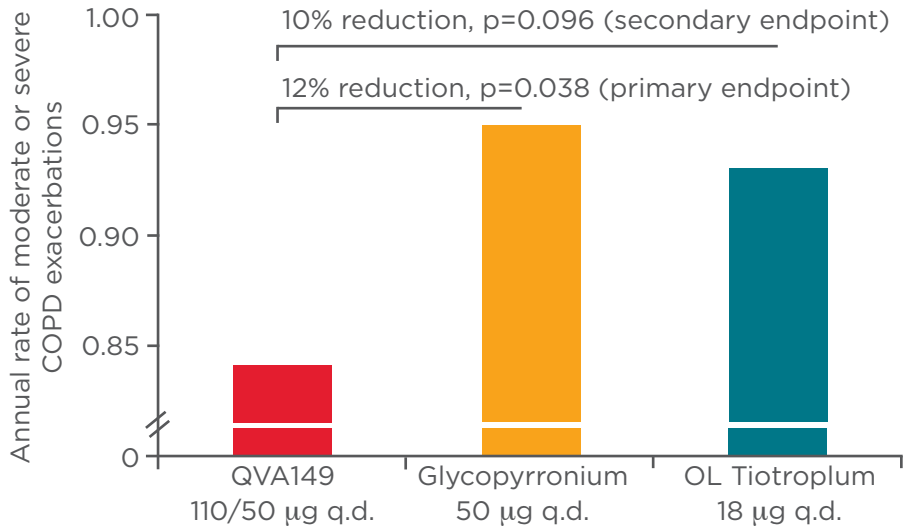
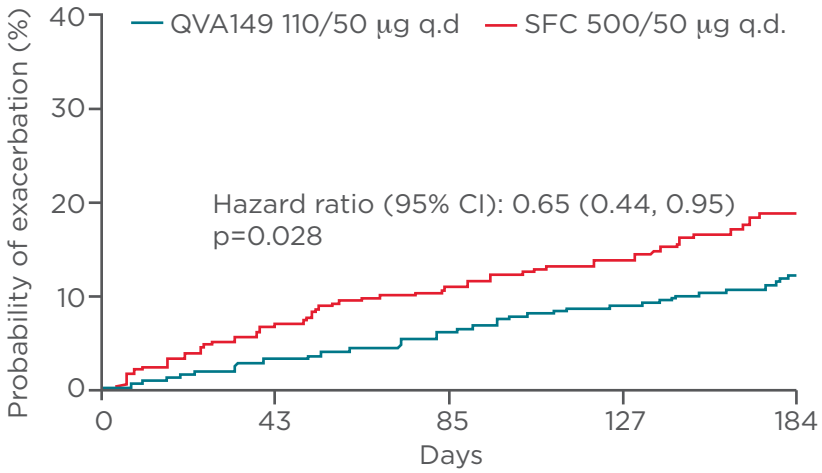


Figure 3: The SPARK study reached its primary endpoint of demonstrating superiority of QVA149 compared with glycopyrronium for the annualised rate of moderate-to-severe chronic obstructive pulmonary disease (COPD) exacerbations during the 64-week treatment period.

q.d.: quaque die (once daily); OL: open label.

Adapted from Lancet Respiratory Medicine, 1, Wedzicha et al., Analysis of chronic obstructive pulmonary disease exacerbations with the dual bronchodilator QVA149 compared with glycopyrronium and tiotropium (SPARK): a randomised, double-blind, parallel-group study, 199–209, 2014, with permission from Elsevier.



Patients with exacerbation (%)					
QVA149	0	12 (3.3)	20 (5.5)	31 (8.6)	43 (12.1)
SFC	0	24 (6.6)	38 (10.5)	48 (13.4)	67 (18.9)

Figure 4: QVA149 significantly reduced the time to first moderate or severe chronic obstructive pulmonary disease (COPD) exacerbation compared to salmeterol + fluticasone in the LANTERN trial.

K-M: Kaplan–Meier; SFC: salmeterol/fluticasone propionate.

Adapted from Zhong N et al.[44]

Conclusions

Professor Bartolome Celli

COPD is a multi-dimensional, complex disease, but various disease characteristics help to assign patients to appropriate groups with therapeutic implications. Even though prognosis can be poor, COPD patients with poor status should be treated aggressively since not all patients decline equally; there are both rapid and non-rapid decliners, with average reduction in FEV_1 of 28 and 86 mL/year, respectively.[46]

Classification of patients into phenotypes may be of some use in order to identify which therapies to use. 'Rapid decliners' are those that are younger and who lose a large degree of lung function; this phenotype has not been studied as much as others. 'Hyperinflated' patients seem to have lung function as their major problem, but do not respond to anti-inflammatories since their disease is not one of severe inflammation. 'Exacerbators' may have to be approached differently to these other categories, and for 'co-morbid' patients COPD is not the driving force, meaning that individual therapy decisions will differ. Based on the COPD treatment algorithms there are now multiple possibilities for pharmacotherapy along with other treatment options such as rehabilitation, lung volume reduction surgery, oxygen supplementation, and azithromycin.

There is a continuing need to promote a healthy lifestyle and reduce smoking and air pollution, and improved diagnosis of COPD is required. Symptomatic patients on monotherapy or LABA/ICS should be considered for dual bronchodilation, and for patients with a high risk of exacerbations the data suggest this may also be a viable treatment option.

Summary of Q&A and Panel Discussion

Short-acting beta antagonists or short-acting muscarinic antagonists should only be used on an as-needed basis, not as a regular therapy.

The safety of LABA/LAMA combination is convincing in both older and younger patients; however, young people need to be active - increasing FEV_1 will improve QoL. Therefore younger patients may particularly benefit from combination therapy. Caution may be advised in prescribing LABAs/LAMAs in patients with significant underlying cardiovascular symptoms.

There is no difference between genders regarding the efficacy of dual bronchodilation.

Macrolides reduce exacerbations, likely through activity on infection but not on inflammation. There are, however, cardiac side-effects, and resistance is acquired quickly; it is suggested to use these drugs seasonally and not for long periods of time.

Theophylline has been used as a fourth-line agent on top of triple therapy, and is used very commonly outside of the USA. It may, however, increase mortality.

More needs to be learnt about when to use LABA/ICS; we now know that, before ICS, we can use LABA/LAMA, and ICS or other anti-inflammatories may be useful on top of dual therapies.

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NOCTURNAL NON-INVASIVE VENTILATION FOR CHRONIC OBSTRUCTIVE PULMONARY DISEASE: A FINAL BREAKTHROUGH?

Summary of Presentations from a ResMed-Sponsored Satellite Symposium, held at the 24th ERS Congress, Munich, Germany, on 8th September 2014

Chairperson

Wolfram Windisch[1]

Speakers

Jean-Louis Pepin,[2] Thomas Köhnlein,[3] Michael Dreher[4]

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Disclosure: Prof Windisch has received open research grants for his hospital and personal speaking fees from companies dealing with mechanical ventilation. Dr Pepin received personal fees from ResMed, Philips, Fisher & Paykel for lectures during congress symposia, and unrestricted grants from ResMed, Philips, and AGIRadom for conducting clinical studies. Dr Köhnlein has received grants and lecture fees from Deutsche Lungenstiftung, ResMed, Tyco, Weinmann, and Heinen und Löwenstein. Dr Dreher receives an open research grant from ResMed, and has received speaking fees and/or fees for advisory boards from: Weinmann, Respironics, Vivisol, Linde, ResMed, Breas, Novartis, Boehringer, Almirall, Actelion, and Chiesi.
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MEETING SUMMARY

Prof Windisch opened the symposium on the efficacy of non-invasive ventilation (NIV) in the treatment of chronic obstructive pulmonary disease (COPD). Dr Jean-Louis Pepin summarised the evidence for efficacy of NIV in subgroups of COPD patients. Dr Thomas Köhnlein focused on a recently-published randomised trial showing a major reduction in mortality following NIV aimed at a marked reduction in carbon dioxide pressure ($PaCO_2$), while Dr Michael Dreher illustrated the place of NIV in patients with recent exacerbations.

Introduction

Professor Wolfram Windisch

Prof Windisch welcomed the audience to the ResMed-sponsored satellite symposium on NIV for COPD. The audience were invited to engage in discussion with the speakers at the end of each presentation.

NIV for Stable COPD: Which Phenotypes can Benefit?

Doctor Jean-Louis Pepin

There is a plethora of data from clinical trials supporting acute in-hospital use of NIV. However, the evidence for domiciliary use of NIV for stable COPD is comparatively weak and there are discrepancies in mortality data between individual randomised controlled trials. Despite this, in

several European countries, chronic hypercapnic respiratory failure (CHRF) due to COPD is a common indication for domiciliary NIV.[1]

Data from the general population of COPD patients are inconclusive. In a recent study by McEvoy et al.,[2] patients with hypercapnic COPD were randomised to receive either nocturnal NIV and long-term oxygen therapy, or long-term oxygen therapy alone. Only a small improvement in survival was demonstrated at the cost of a possible worsening in quality of life (QoL). Furthermore, the survival benefit was only demonstrated in the adjusted and not the unadjusted analysis, bringing its validity into question.[2] In another trial, unselected patients with COPD were treated with NIV or standard care. Immediately, or several weeks after exacerbation, there was an improvement in blood gases but no survival advantage in the NIV-treated group. However, it is likely that the adverse effect of acute respiratory failure in terms of prognosis outweighed any benefit of NIV in this setting.[3]

Results from a recent trial suggest that a subgroup of patients with stable COPD do respond to NIV. The study compared NIV aimed at a 20% reduction in partial $PaCO_2$ with standard care and showed a substantial improvement in survival and QoL in the NIV group.[4] When considering the appropriate use of NIV, it is important to understand that COPD is not a homogenous condition. The two most common phenotypes are respiratory COPD, characterised by low body mass index (BMI), severe respiratory COPD, and hyperinflation; and systemic COPD with less airway obstruction but with multiple comorbidities often including overlap syndrome (COPD and obstructive sleep apnoea [OSA]). COPD subtypes are associated with different prognoses and causes of hospitalisation, as reported in a recent study showing that all-cause mortality was higher in exacerbations of severe respiratory COPD.[5] In the systemic COPD subgroup, the main reason for hospitalisation was cardiovascular, while patients with the respiratory phenotype were more likely to be admitted due to COPD.[5] These differences in prognosis and phenotype may underlie differences in the response to NIV.

In patients with overlap syndrome, a classical picture of OSA during non-rapid eye movement (REM) sleep, and oxygen desaturation and increased transcutaneous CO_2 during REM sleep, is frequently observed.[6] A study by Marin et al.[7] revealed increased all-cause mortality and hospitalisation due to exacerbation in patients with overlap syndrome compared to those with COPD alone. In patients whose OSA was treated with NIV, the increases in mortality and exacerbation-related hospitalisation were ameliorated. A more recent study indicates that the survival benefit of NIV is restricted to hypercapnic patients, with no benefit in normocapnic patients.[8]

NIV settings are more difficult to adjust in severe respiratory COPD with hyperinflation, and thus, the response to NIV may be affected in this patient subgroup. Asynchronous ventilation caused by inappropriate settings in these patients appears to result in progressively increased hyperinflation and discomfort upon waking. In a study by Adler et al.,[9] calibrated adjustments resulted in decreased pressure support and tidal volume, with increased respiratory rate. These changes were associated with improvements in daytime $PaCO_2$, morning dyspnoea, and sleep quality.

In a recent prospective observational cohort study directly comparing patients with respiratory or systemic COPD, the rate of hospitalisation and death was lower in patients with systemic COPD than in the respiratory COPD group. Despite reasonably high adherence rates in both groups, as indicated by time spent on NIV, patients with systemic COPD had significantly longer mean daily use of NIV (6.9 versus 5.5 hours/day, respectively; Figure 1).[10] Data from a recently-published meta-analysis suggest that changes in daytime $PaCO_2$ are related to the duration of NIV.[3] These differences in adherence may partly explain differences in response to NIV.

Studies investigating the efficacy of NIV should not focus solely on mortality as an endpoint. In patients with recurrent acidotic exacerbations of COPD, NIV reduced the number and duration of admissions as well as the total days spent in hospital. These beneficial effects were associated with cost reductions of >50%.[11]

In summary, stable COPD patients are not a homogeneous population, and thus the question of whether these patients respond to NIV requires refinement. Prognostic differences and distinct causes of death and hospitalisation are apparent between phenotypes of stable COPD patients, and studies indicate that these subgroups may respond differently to NIV. Differences in adherence are also likely to have a role in determining the response to NIV in terms of both efficacy and overall

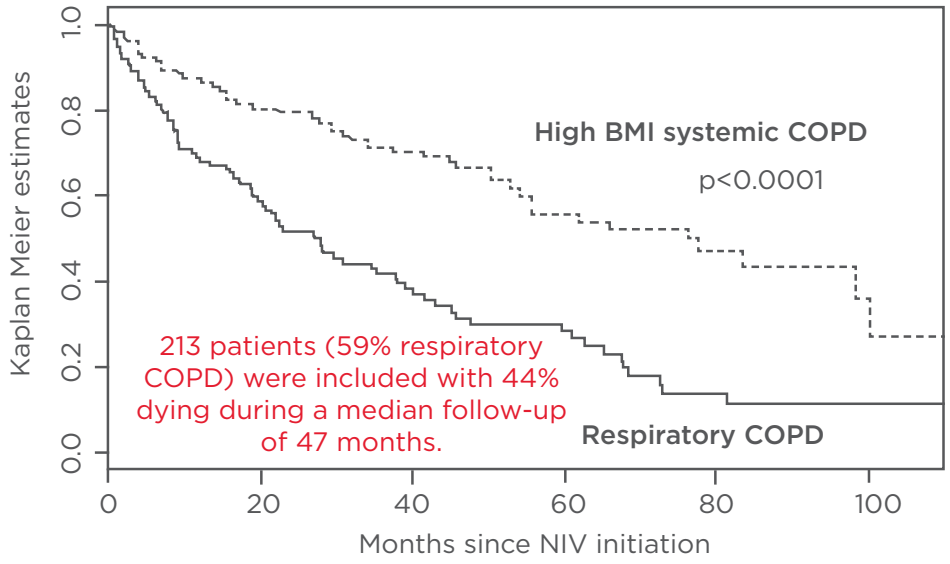
mortality. Researchers should not focus solely on mortality as an outcome and should be aware of other considerations such as cost reductions associated with NIV use. The above considerations suggest that future randomised trials should focus on subgroups of COPD patients who have a higher likelihood of response to NIV. Data from prospective registries, such as the European Home Mechanical Ventilation Registry, which is focused on domiciliary NIV, will be useful in directing future research.

Home NIV for COPD: a Final Breakthrough?

Doctor Thomas Köhnlein

The genesis of the Non-invasive Ventilation in Severe COPD trial (NCT00710541), summarised here, was the disconnect between clinical experience and the results of previous trials showing a lack of efficacy for NIV in stable COPD.[4] The investigators took a novel approach by focusing their hypothesis on achieving the marked reduction in hypercapnia that they believed would be required in order for NIV to show efficacy, and thus improve survival in patients with advanced, stable hypercapnic COPD. The primary outcome was overall mortality. Secondary outcomes included blood gases, changes in hypercapnia, oxygenation, 6-minute walking distance, and QoL measures.

The trial was a multicentre parallel-group study powered at 150 patients per group with a 1-year follow-up. Inclusion criteria included COPD in Global Initiative on Obstructive Lung Disease (GOLD)-Stage 4; $PaCO_2$ 7 kPa (51.8 mmHg) or higher, and pH >7.35, assessed during spontaneous breathing; and a stable disease state with no change in medication for ≥4 weeks. These criteria were aimed at recruiting a patient population at low risk of exacerbation or hospitalisation, with moderate-to-severe COPD and ventilatory insufficiency, ruling out any other respiratory disorders. Investigators set themselves the challenging target of achieving a sustained 20% reduction in hypercapnia after 1 hour of spontaneous breathing, post-NIV. Ventilator settings were left to investigator discretion and patients were asked to use their machines for ≥6 hours per day. In total, 195 patients were randomised, 93 patients in the control arm received standard care, and 102 patients in the intervention group received standard care plus NIV aimed at a 20% reduction in hypercapnia (Figure 2).



No. of patients at risk

Non-Obese	111	61	30	17	6	2
Obese	102	81	57	35	17	4

Figure 1: Rate of hospitalisation and death following initiation of NIV.
NIV: non-invasive ventilation; BMI: body mass index; COPD: chronic obstructive pulmonary disease.
Borel JC et al.[10]

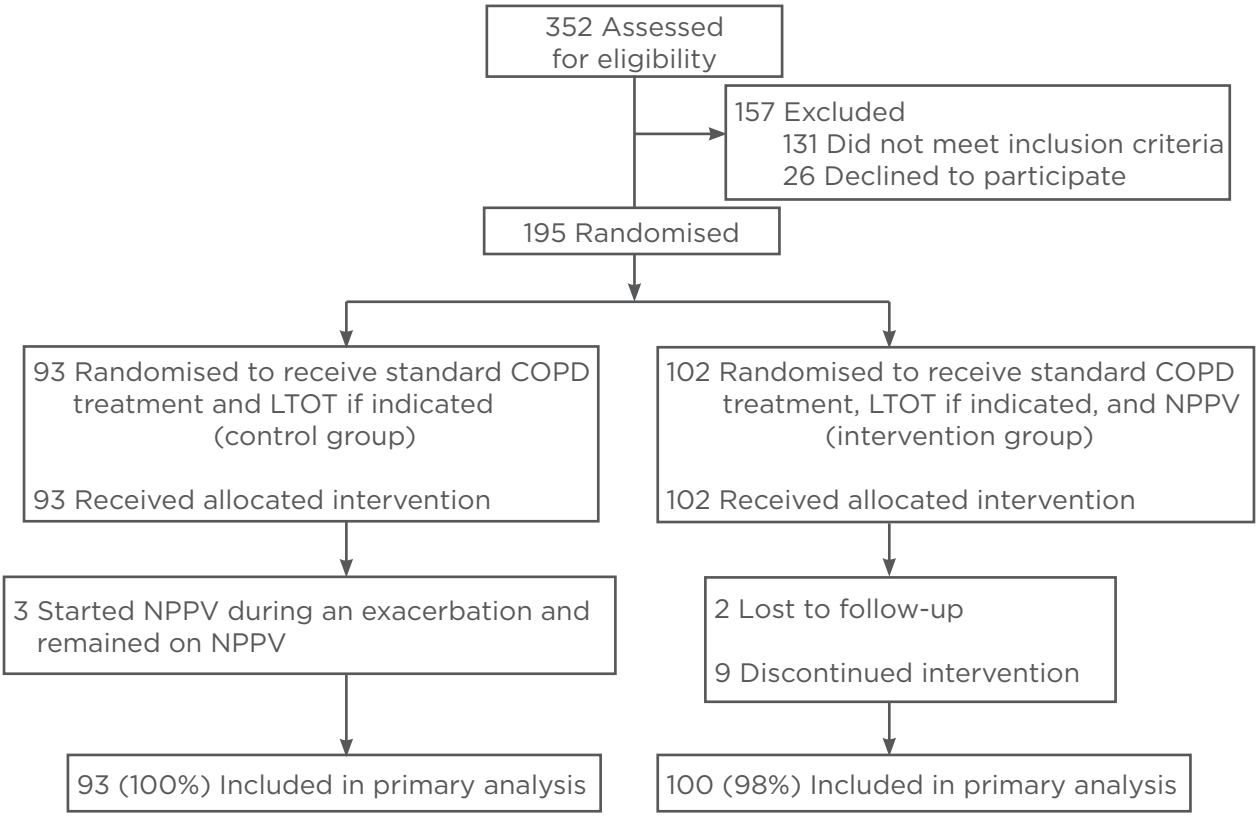


Figure 2: Patient disposition through the randomised controlled trial of non-invasive ventilation versus standard care.

COPD: chronic obstructive pulmonary disease; LTOT: long-term oxygen therapy; NPPV: non-invasive positive pressure ventilation.

Köhnlein T et al.[4]

Patients were well balanced in terms of baseline characteristics: predominantly male, with a mean age of approximately 64 years. Mean BMI was 24–25 kg/m^2 and there were no cases of obesity hypoventilation syndrome.[12] Lung function was as expected for GOLD–Stage 4 patients (forced expiratory volume in 1 second [FEV_1] 26-28% of predicted), patients were not acidotic, and baseline $PaCO_2$ was 7.7 kPa and 7.8 kPa in the control and intervention groups, respectively (approximately 58 mmHg). Both groups showed elevated bicarbonate (HCO_3-) levels (approximately 34 mmol/L), indicative of chronic hyperventilation. Approximately 65% of patients in each group were on long-term oxygen at baseline.

After 1 year of treatment, patients receiving NIV had mean inspiratory and expiratory pressures of 21.6±4.7 and 4.8±1.6 cmH_2O, respectively. The mean back-up frequency was 16 breaths/minute, with 70 of the 102 ventilated patients having back-up frequency settings indicative of controlled ventilation (≥14 breaths/minute). The mean daily duration of NIV was 5.9±3.1 hours, slightly below target.

There was a marked reduction in $PaCO_2$ (≈16%) after 14 days, which remained stable for the duration of the trial but did not reach the desired 20% threshold (Figure 3). Notably, the 14 days during which ventilation settings were calibrated was the period during which the reduction in $PaCO_2$ occurred in the intervention group, and there was little change after this period despite ventilation throughout the study. It is also worth noting that there was a slight improvement in $PaCO_2$ in the control group, perhaps due to improved compliance with standard care.

There was a statistically and clinically significant 35-metre (14%) increase in 6-minute walking distance in the intervention group, which was evident after 14 days, and it remained relatively stable throughout the study.[13] There was no meaningful change in health-related QoL (measured using the St George's Respiratory Questionnaire

[SGRQ]) in the control group, but there was a small, but clinically relevant, 5-point improvement in SGRQ score in the intervention group. The mental component of the generic Short Form-36 questionnaire also showed a statistically significant improvement in the intervention group, but there was no change in the physical summary score. The Severe Respiratory Insufficiency (SRI) questionnaire is specifically designed to assess health-related QoL in patients receiving either invasive or non-invasive long-term ventilation. An improvement in the SRI score, similar to that seen in previous studies, was achieved in the intervention group.[14] In summary, QoL improvements were documented using disease-specific tools, which are more likely to reflect true changes in QoL.[14]

As the primary outcome, overall mortality was higher than expected in the control group (Figure 4), but there was a highly significant reduction in mortality in the intervention group after 1 year (12% versus 33%, respectively). Although it should be noted that the study is somewhat underpowered, this signal is clear enough to indicate a decisive survival advantage with chronic NIV treatment in patients with stable hypercapnic COPD. Investigators have continued to follow patients and the survival advantage appears to persist up to 5 years, although these data should be viewed with caution given the small population size and the fact that the study was not powered for this duration of follow-up. It is notable that the majority of the between-group difference in mortality rate occurred during the first month of the study, similar to the pattern seen for other outcomes; survival lines remained approximately parallel from month 6 onwards throughout the remainder of the extended follow-up.

These data show a clear survival signal with NIV when treatment is aimed at achieving a marked reduction in $PaCO_2$. Further studies building on these results will help to better define the place of this NIV strategy in the treatment of stable COPD.

One major point covered during the discussion, following the above presentation was why the control group mortality rate was so high. Currently there is no clear answer; indeed it was found later that the Data Safety Monitoring Board had considered stopping the trial early, but did not believe that the trend of high mortality in control patients would continue. All patients were followed until the 1-year time point or death, and there was no clear signal from death certificates or from medical reports despite numerous pneumonias, cardiac arrests, and infections.

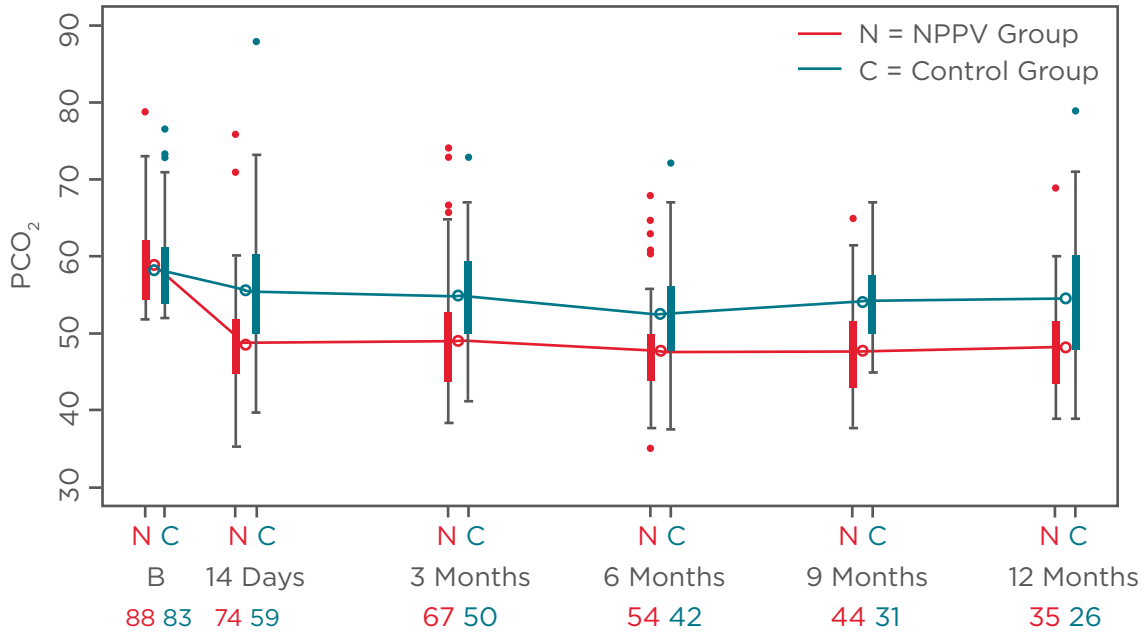


Figure 3: Change in $PaCO_2$ in NIV versus standard care in patients with stable COPD.
NPPV: noninvasive positive pressure ventilation; NIV: non-invasive ventilation; COPD: chronic obstructive pulmonary disease; $PaCO_2$: partial pressure of carbon dioxide.
Köhnlein T et al.[4]

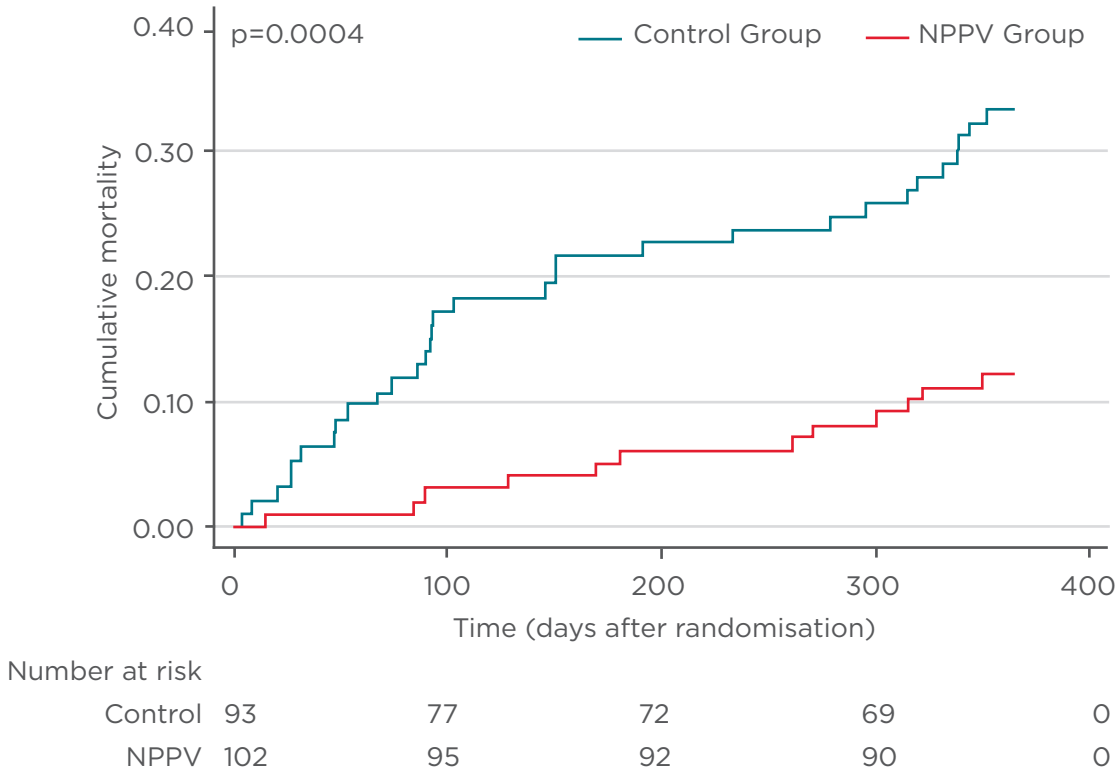


Figure 4: Overall mortality for treatment with NIV versus standard care in stable COPD.
NIV: non-invasive ventilation; COPD: chronic obstructive pulmonary disease; NPPV: noninvasive positive pressure ventilation.
Köhnlein T et al.[4]

Some deaths were attributed to COPD in general, but no specific cause of death was documented in these patients. Indeed, the issue of what ultimately causes death in COPD patients is a difficult topic. The underlying cause of death is often difficult to identify and the precision of medical reports, at least in the above German setting, is currently inadequate for this purpose.

Case Reports: What can we Learn from Daily Practice?

Professor Michael Dreher

In order to illustrate what can be learned about treating COPD from daily practice, two case studies were presented. The first case was that of a 72-year-old male patient, a former smoker, with COPD in GOLD Stage 4. FEV_1 was 19% of predicted, total lung capacity (TLC) was 137% predicted (indicative of severe emphysema), and exacerbations were frequent. The patient had received 6 years of domiciliary NIV by 2009, a year in which he was admitted to hospital eight times with acute hypercapnic respiratory failure (AHRF). The mortality risk in such a patient with very severe COPD and more than bi-monthly hospitalisations is extremely high, particularly given of the link between repeated exacerbations and increased mortality.[15] The patient refused to be transported to hospital without continuous ventilation from his own device during incidents of acute exacerbation he would administer ventilation for 18–24 hours/day.

On admission with an acute hypercapnic exacerbation in November 2009, the patient presented with no fever, no elevation in C-reactive protein (CRP) levels, increased dyspnoea, and increased time on NIV (24 hours); pH was 7.29 and $PaCO_2$ was nearly 75 mmHg. The patient had been receiving NIV for several years with an inspiratory positive airway pressure of 28.6 cmH_2O and an expiratory positive airway pressure of 4.1 cmH_2O. Inspiration time was 1 second and breathing frequency was 18 $minute^{-1}$. The patient refused entry to the intensive care unit (ICU), he was prescribed prednisolone, and was discharged after 6 days

on the respiratory ward, during which ventilation time was gradually reduced. This single case illustrates the potential for home NIV to ameliorate AHRF, with the patient effectively copying the treatment they will later receive in hospital.

Another exacerbation episode in this patient, although different from the events described above, also illustrates an important point. The patient declined admission to the ICU and, unfortunately, died. When patients have such a strong personal engagement with their treatment, it is essential to agree plans in advance on how to proceed in case of deterioration to allow the possibility of admission to ICU or other appropriate measures.

The second case was a 57-year-old male with COPD GOLD-Stage 4, who had a BMI of 17 kg/m^2, an FEV_1 36% of predicted, and a high TLC (119% of predicted). He had been on long-term oxygen for 3 years and his breathing was rapid and shallow, with a frequency of 38 minute^{-1}. The patient presented with a silent lung due to emphysema, fever, elevated CRP (156 mg/dL), and no infiltrates detected on chest X-ray. Blood gas analysis (5 L oxygen [O2]/min) showed a pH of 7.21, PaO_2 of 59 mmHg, $PaCO_2$ of 78 mmHg, and HCO_3- of 29 mmol/L, indicating AHRF with respiratory acidosis. The patient was referred to the ICU, NIV was set up, and his blood gases were controlled at $PaCO_2$ 82 mmHg and pH 7.2. He was acutely ventilated with inspiratory pressure levels incrementally increased from 15.3 to 21.4 cmH_2O, and expiratory levels incrementally increased from 4.1-6.1 cmH_2O, FiO_2 was 45%. pH significantly improved over time and $PaCO_2$ fell from 82-62 mmHg.

The patient was discharged from the ICU after 3 days with no fever and reduced CRP, dyspnoea, and breathing frequency. Blood gases (3 LO_2/min) were now at pH 7.36, $PaCO_2$ 54 mmHg, and HCO_3- 30 mmol/L, indicating CHRF. The patient was referred to the respiratory ward and overnight blood gases (2 LO_2/minute) showed a slight increase in $PaCO_2$ to 58 mmHg, with pH 7.37, PaO_2 59 mmHg, and HCO_3- 29 mmol/L. Again, these results are indicative of CHRF. The question for physicians was whether to begin domiciliary NIV. As the patient had CHRF and this was his first admission to hospital, attending physicians discharged him from the respiratory ward after 4 days with no fever, normal CRP levels, and a 3-day course of oral corticosteroids. Readmission was planned for control of blood gases and an evaluation of the need for domiciliary NIV. The patient returned to hospital after 6 weeks showing mild hypercapnia ($PaCO_2$ 46.3 mmHg). Night-time levels were slightly higher (49.8 mmHg) and it was determined that there was not an indication for domiciliary NIV.

In summary, domiciliary NIV may reduce the severity of AHRF if the treatment mirrors that likely to be received in hospital. NIV after AHRF is not necessary in all hypercapnic COPD patients, but lack of recovery after 6 weeks may be a good indicator that NIV is required.

Meeting Close

Professor Wolfram Windisch

Prof Windisch thanked the speakers for their presentations as well as the audience for their questions and discussion points. With a final thank you to ResMed for having organised the symposium, the meeting was brought to a close.

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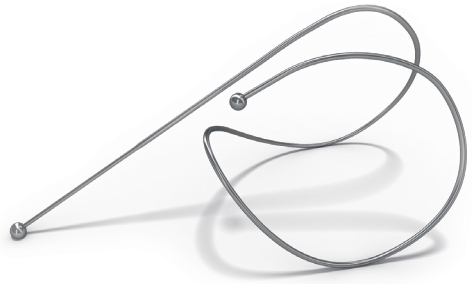

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NEW EVIDENCE AND NOVEL THERAPIES FOR SEVERE ASTHMA MANAGEMENT

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ABSTRACT

The 2014 European Respiratory Society International Congress, held last month from 6th-10th September in Munich, Germany, provided a platform for key opinion leaders in the field of asthma management to disseminate new clinical data and recent developments. Despite the use of high-dose inhaled corticosteroids and long-acting β_2 agonists, a proportion of patients still have uncontrolled disease and are at risk of exacerbation and hospitalisations, thus requiring the use of intermittent or continuous oral corticosteroid therapy. In severe uncontrolled asthma, exacerbations can be potentially life-threatening, and are the main cause for morbidity and mortality in asthma patients, necessitating considerable healthcare resource utilisation. Consequently, there remains an unmet need for newer therapies to manage asthma in several patient subsets, for which current therapeutic options do not yield adequate benefits and outcomes.

Keywords: Asthma, omalizumab, QGE031, ligelizumab, reslizumab, mepolizumab, QAV680, QMF149, QAW039, fevipiprant.

INTRODUCTION

The 2014 European Respiratory Society International Congress, held last month from 6th-10th September in Munich, Germany, provided a platform for key opinion leaders in the field of asthma management to disseminate new clinical data and recent developments. Asthma is a common chronic inflammatory disease affecting >300 million people worldwide,[1] and is associated with a considerable economic burden and impaired quality of life (QoL).[2] The most prevalent form of asthma is allergic asthma, accounting for two-thirds of the patient population.[3-5] Despite the use of high-dose inhaled corticosteroids (ICS) and long-acting β_2 agonists (LABAs), a proportion of patients still have uncontrolled disease, and are at risk of exacerbation and hospitalisations,[6-8] thus requiring the use of intermittent or continuous oral corticosteroid (OCS) therapy. In severe uncontrolled asthma, exacerbations can be potentially life-threatening and are the main cause for morbidity and mortality, necessitating considerable healthcare resources utilisation (HCRU).[9-11] Consequently, there remains an unmet need for newer therapies to manage asthma in several patient subsets, for which current therapeutic options do not yield adequate benefits and outcomes.[12] This review will summarise newly presented preclinical and clinical data at ERS 2014, providing further information on the efficacy and safety of new and emerging therapies for asthma.

NEW EVIDENCE ON QMF149 (INDACATEROL ACETATE/ MOMETASONE FUROATE)

QMF149 is an investigational once-daily (OD) inhaled bronchodilator (BD) fixed-dose combination (FDC) of indacaterol acetate (IND), a LABA, and mometasone furoate (MOM), an ICS, for the maintenance and treatment of asthma and chronic obstructive pulmonary disease (both compounds are already approved as monotherapeutic modalities). The FDC is delivered via the low-resistance Breezhaler® device.

New Clinical Data on the Efficacy and Safety of Indacaterol

In a 12-week multicentre, randomised, double-blind, placebo-controlled, parallel-group study[13] aiming to support the dose selection of IND for QMF149 in asthma, Beier et al.[13] assessed the effects of OD IND 150 µg and 75 µg compared with placebo in a cohort of 335 patients with persistent asthma, randomised (1:1:1) to one of these three treatment arms. The main endpoint was trough forced expiratory volume in 1 second ($tFEV_1$) at 12 weeks. The IND 150 µg OD and IND 75 µg OD treatment arms demonstrated statistically significant (106 ml, $p<0.002$ and 80ml, $p<0.019$) improvements in $tFEV_1$ compared with placebo after 12 weeks of therapy. From day 2 and onwards, for all time points, IND 150 µg OD was statistically superior to IND 75 µg OD (67 ml, $p=0.018$). However, the statistical power of the study was not sufficient to establish a statistically significant difference between both doses. Other endpoints demonstrated a clinically meaningful superiority of both IND doses over placebo, namely peak expiratory flow rate, asthma control questionnaire (ACQ)-5, and rescue medication use. Overall, a low incidence of adverse events (AEs) was observed in all treatment arms.

New Preclinical Data on the Pharmacokinetics of QMF149

In a randomised, open-label, four-way crossover study,[14] the pharmacokinetics of the components of QMF149, IND, and MOM were assessed, in order to determine the possibility of a pharmacokinetic or a biopharmaceutical interaction between both compounds. Their steady-state pharmacokinetics, as well as safety and tolerability, were evaluated in 64 healthy subjects receiving IND 150 µg, MOM 320 µg, a free combination (IND 150 µg + MOM 320 µg), or a FDC of QMF149 150/320 µg (IND/MOM) OD for 14 days. The results regarding systemic exposure did not reveal any pharmacokinetic interaction between IND and MOM, or any clinically relevant differences, as demonstrated by similar geometric mean ratios between QMF149 and the free combinations or IND and MOM as monotherapy. Likewise, all modalities were well tolerated, which supports the development of QMF149 as an FDC without any need for dose adjustment.

NEW CLINICAL EVIDENCE ON MONOCLONAL ANTIBODY THERAPY FOR ALLERGIC ASTHMA

New Clinical Evidence on Omalizumab

Omalizumab (Xolair®, Roche/Genentech, and Novartis) is a humanised monoclonal antibody that is already approved for the treatment of moderate-to-severe persistent allergic asthma that is not responding to high-dose ICS + LABA therapy. It has demonstrated clinical activity in reducing asthma exacerbations and use of ICS in patients with allergic asthma.[15-19]

New clinical evidence on predictive tools to treatment response

The global evaluation of treatment effectiveness (GETE) at 16 weeks is a tool used in clinical practice to evaluate the clinical response to omalizumab with regards to the control rate of asthma exacerbations in patients with uncontrolled severe asthma.[20] Bousquet et al.[21] presented the results of a study aiming to explore the GETE as a predictive tool and as an accurate predictor of response to omalizumab therapy. In a post-hoc analysis, the authors pooled the data (omalizumab arms, n=947; placebo arms, n=660) from three pivotal clinical trials: INNOVATE,[7] EXALT,[20] and EXTRA,[6] which explored the use of omalizumab in severe allergic asthma patients. In the negative binomial regression model, investigator GETE response was an accurate predictor of asthma exacerbations as well as response to omalizumab versus placebo ($p<0.001$). Annualised exacerbation rates (0.29) were significantly lower in patients responding to the GETE (defined as 'good' or 'excellent' score) and who received omalizumab, as compared with non-responding patients in the omalizumab group (0.67) and patients in the placebo group (responders, 0.46; non-responders, 0.78). In conclusion, these results are consistent with the results presented by Kasujee et al.;[22] GETE assessment at 16 weeks may be an effective predictive tool of response to omalizumab therapy, but further studies are required to confirm these findings.

New clinical evidence on the risk of asthma exacerbations

In a post-hoc analysis,[22] the treatment effects of omalizumab, as evaluated by the GETE, were assessed in moderate-to-severe persistent allergic

asthma, and comprised data (omalizumab arms, n=858; placebo arms, n=901) from five randomised, double-blind, pivotal registration trials, including the INNOVATE and SOLAR studies.[7,16-18,23] The results of this analysis established the role of omalizumab in reducing exacerbation rates for GETE-responders. Omalizumab GETE-responders had significantly lower (-51%) annualised exacerbation rates than placebo responders. These results further support the use of GETE assessment as a predictive tool for response to omalizumab therapy, and may help to select patients who would most benefit from this therapeutic option.

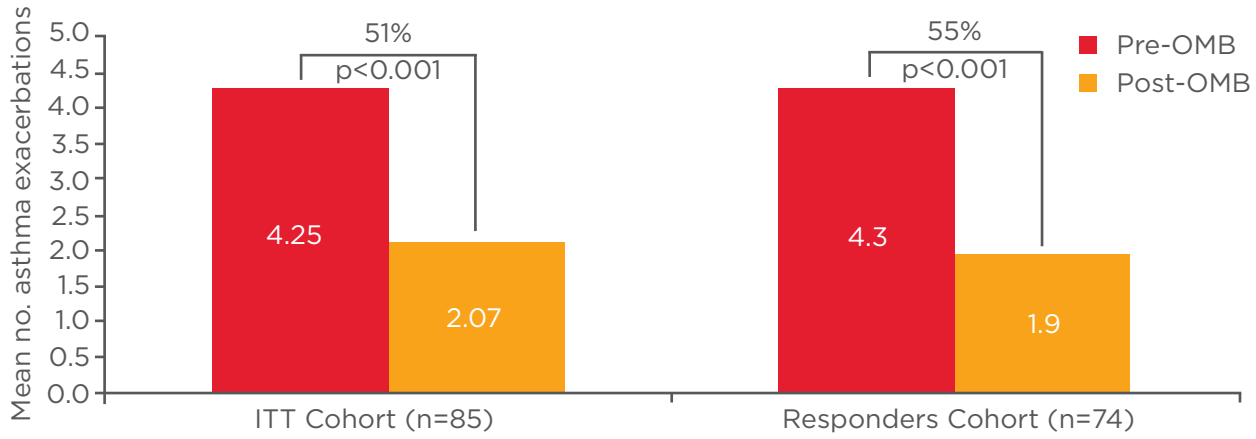

Figure 1: Mean number of asthma exacerbations per patient in the 12 months before and after starting omalizumab (OMB) in the intent-to-treat (ITT) (n=85) and responder (n=74) cohorts.[24]

ITT cohort: patients with 12 months of assessment at interim analysis; Responder cohort: patients classified as responders to treatment by their clinician at 16-week assessment.

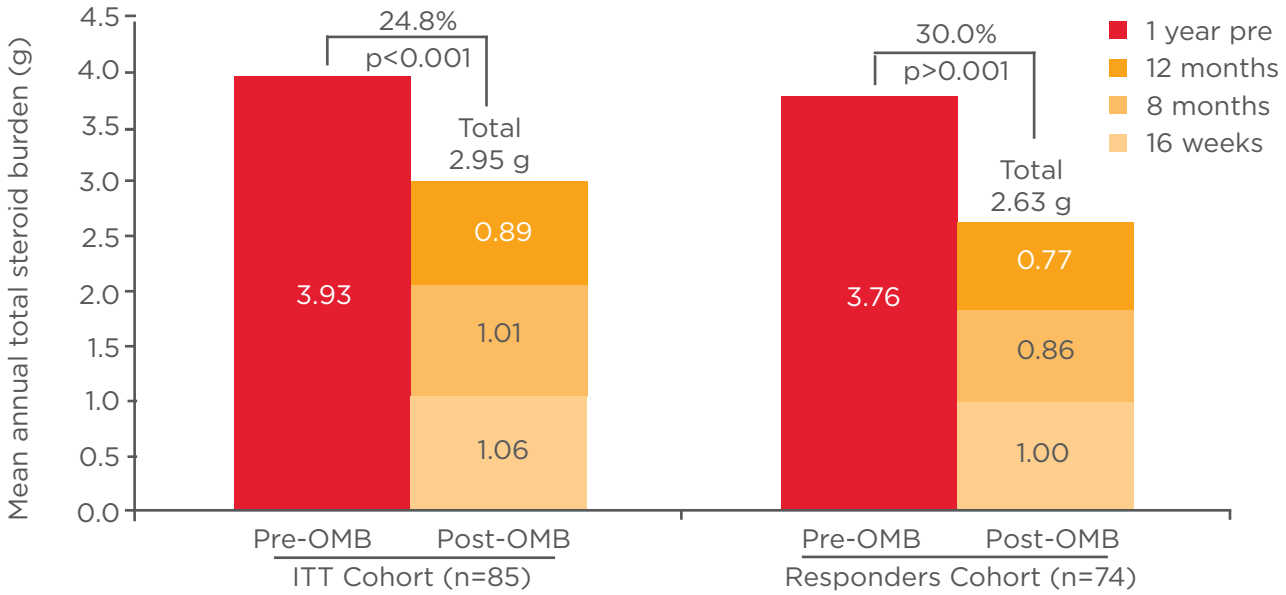

Figure 2: Total per-patient use of oral corticosteroids (OCS) in the 12 months pre and post-omalizumab (OMB) initiation in the intent-to-treat (ITT) (n=85) and responder (n=74) cohorts.[26]

ITT cohort: patients with 12 months of assessment at interim analysis; Responder cohort: patients classified as responders to treatment by their clinician at 16-week assessment.

The APEX study: clinical evidence on exacerbations, lung function, and OCS use

The APEX II study was a multicentre observational study evaluating the role of omalizumab in asthma control, OCS burden, HCRU, and patient-reported outcomes in 235 UK patients, across 22 centres, suffering from severe allergic asthma. This study is particularly interesting because it provides real-world data on the impact of omalizumab therapy in daily clinical practice. Interim analysis results at 12 months (n=85) were presented at ERS 2014; data were reported on exacerbation rates, lung function, and OCS use following omalizumab therapy.

The mean number of exacerbations was significantly reduced in the first 12 months post-omalizumab, as compared with the 12-month period prior to therapy (2.07±2.01 versus 4.25±2.73, -51%, p<0.001; Figure 1).[24] Similar and statistically significant decreases were also observed in terms of hospitalised asthma exacerbations and healthcare utilisation. Lung function, as assessed by FEV_1, was overall (average on the 12-month period) significantly improved in both the intent-to-treat (ITT) population (+7.78% predicted, p<0.001) and patients who responded to omalizumab therapy (n=75; +8.86% predicted, p<0.001; Table 1).[25] In the ITT and responders populations, isolated assessment analyses at 16 weeks (+14.14% and +9.68%, respectively; p<0.001 for both groups) and 8 months (+13.84% and +11.07%, respectively; p<0.001 for both groups), post-omalizumab initiation, yielded similar results. However, 12-month data differences were not significant (+4.41% and +5.32%, respectively; p>0.1 for both groups). The annual OCS use in the first 12 months following omalizumab therapy was significantly decreased in comparison to OCS use prior to omalizumab treatment (-0.97g [-24.8%] of prescribed OCS daily dose, p<0.001; Figure 2). In the responder cohort, this difference is even more pronounced (-1.13g [-30.0%] of prescribed OCS daily dose, p<0.001).[26] During the first 12 months after treatment initiation, 54.8% of patients stopped OCS therapy, while 57.7% of patients reduced their OCS dose by 20% or more.

The XPORT study: clinical evidence regarding long-term therapy and outcomes

While there are a lot of available clinical or real-life data on the efficacy and safety of omalizumab in the short term (up to 12 months),[7,16,17,27] there are limited data on the long-term use of omalizumab and the persistency of response to this treatment modality. XPORT was a Phase IV, multicentre, randomised, double-blind, placebo-controlled study aiming to evaluate the persistency of response to omalizumab (n=88) versus placebo (n=88) in patients with moderate-to-severe persistent allergic asthma, who continued (omalizumab arm) or who discontinued omalizumab (placebo arm) after long-term treatment (5 years and over).[28] Key results demonstrated that continuation of therapy after 5 years allowed for additional benefits in terms of exacerbation and symptom control, as compared with the placebo group. 67.0% of patients in the omalizumab group had a persistency of response, as compared with 47.7% in the placebo arm. The occurrence of AEs or serious AEs was similar between both arms, and the safety profile of omalizumab was consistent with regards to the approved label.

Table 1: Suggestions for reversal of target-specific oral anticoagulants.

Parameter	Dabigatran	Apixaban	Rivaroxaban	Edoxaban
3-factor PCC	Unclear	Unclear	Unclear	Unclear
4-factor PCC	Possible (activated)	Possible	Possible	Possible
Activated factor VIIa	No	No	No	No
FFP	No	No	No	No
Haemodialysis	Yes	No	No	No
Hemoperfusion with activated charcoal	Yes	Possible	Possible	N/A
Oral activated charcoal	Yes	Yes	Yes	N/A

FFP: fresh frozen plasma; PCC: prothrombin complex concentrate.
Updated after Kaatz et al.[24]

New Clinical Evidence on QGE031 (Ligelizumab) versus Omalizumab

In a Phase IIa, exploratory parallel group, double-blind, placebo-controlled study, the relative efficacy and safety of QGE031 (3 subcutaneous [SC] dose groups) was compared to those of omalizumab or placebo, in 37 patients with mild atopic asthma. At 12 weeks, bronchial provocation testing revealed an increased tolerance (by approximately 3-fold) towards inhaled allergen in bronchial provocation testing (change from baseline in the concentration of inhaled allergen leading to a 15% decline in FEV_1) for the two higher QGE031 doses tested (72 mg and 240 mg dosed every 2 weeks), as compared with omalizumab; due to the small sample size of this exploratory trial, the results were only statistically significant for the comparison with the placebo arm.

New Clinical Evidence on Reslizumab and its Relative Efficacy in Relation to Eosinophilia

Corren et al.[29] presented very interesting findings of a double-blind, 16-week, placebo-controlled, Phase III study evaluating the efficacy and safety parameters of reslizumab (Cinquil®, Teva, Petah Tikva, Israel), an investigative anti-interleukin (IL)-5 antibody, in subjects aged 18-65 years with uncontrolled asthma. The findings revealed significant improvements in lung function (FEV_1) over placebo (+68 ml from baseline between both treatment arms). When stratified according to eosinophilia, patients with higher eosinophil blood counts and who were treated with reslizumab presented the highest improvements. The safety profile of reslizumab was mild-to-moderate in severity and was consistent with that reported for the placebo group.

New Clinical Evidence on Mepolizumab

The SIRIUS study

In the SIRIUS study,[30] a randomised, double-blind, placebo-controlled trial, the investigative monoclonal antibody mepolizumab (n=69) was administered as monthly 100 mg SC injections for 6 months and evaluated, versus placebo (n=66), in patients with severe, OCS-dependent asthma. In the active treatment arm, the steroid-sparing effect of mepolizumab was greater than the placebo: 54% versus 33% of patients achieved a dose reduction of 50%. The median OCS dose reduction from baseline was 50% in the mepolizumab group and 0% in the placebo group (p=0.007), while patients receiving mepolizumab experienced a 32% decrease in the rate of exacerbations, despite OCS dose reduction. These findings suggest that in patients with severe eosinophilic asthma, OCS dose could be reduced with concurrent mepolizumab administration while maintaining exacerbation management, which could improve the benefit-to-risk ratio experienced by these patients who often present with AEs due to long-term OCS.[31]

The MENSA study

In a 32-week randomised, double-blind, double-dummy study, mepolizumab therapy (intravenous [IV] or SC injection) was evaluated for efficacy and safety parameters against placebo.[32] 576 patients with severe eosinophilic asthma were randomised to three treatment arms: mepolizumab IV or SC, and placebo. The rate of reduction in exacerbations was statistically significant and greater in the mepolizumab arms (53% and 47%, respectively; p<0.001 for both arms) when compared with the placebo arm. Similar results were observed with respect to lung function (FEV_1) and QoL (St. George's Respiratory Questionnaire). The safety profile of mepolizumab was comparable to that of the placebo.

New clinical evidence on benralizumab therapy for uncontrolled eosinophilic asthma

Benralizumab (n=80) was evaluated against placebo (n=82) in a double-blind Phase II study conducted in patients, stratified by eosinophil blood count, with uncontrolled asthma and receiving ICS therapy.[33] The findings revealed that benralizumab therapy reduced the annual asthma exacerbation rate while improving (statistically significant differences) lung function (FEV_1) and asthma control (ACQ-6), when compared to placebo.

The pharmacoeconomics of allergic asthma

As stated earlier, asthma is associated with a high economic burden, particularly in allergic asthma. Available literature has already explored omalizumab's impact on resource utilisation;[34,35] few data are available on the HCRU of patients at initiation of therapy with omalizumab. In a retrospective study, Baldwin et al.[36] explored the demographic, clinical, and HCRU characteristics of allergic asthma patients. Increasing HCRU (emergency room visits, urgent care, or hospitalisations) in the year before omalizumab

therapy was detected, in comparison with the 13-24 months prior to therapy initiation. The patients with moderate asthma presented larger proportional increases in HCRU than patients with severe asthma.

NOVEL AND EMERGING THERAPIES TARGETING THE CRTH2 RECEPTOR FOR UNCONTROLLED ASTHMA MANAGEMENT

QAV680 and QAW039 (fevipiprant) are selective, competitive, and reversible oral CRTh2 receptor antagonists; the former has been investigated in allergic diseases, particularly in allergic rhinitis,[37] and the latter is currently being investigated in Phase II studies for uncontrolled asthma.

New Preclinical Data on QAV680 and QAW039

Pharmacological characterisation of QAV680 and QAW039

At ERS 2014, Willard et al.[38] presented the detailed *in vitro* and *in vivo* pharmacological characterisation and the evaluation of *in vivo* pharmacokinetic profiles of QAW039 and QAV680. Both compounds possess a high selectivity for the CRTh2 receptor, and inhibit eosinophil shape change (i.e. their activation) and IL-5 and 13 production by Th2 cells. The data suggest that QAW039 is much more potent than QAV680 with regards to these assays.

Pharmacokinetics and safety of QAW039 in healthy subjects

Sykes et al.[39] described the receptor binding kinetics of QAW039 and compared them to other CRTh2 antagonists, including QAV680. The authors observed an improved duration of action for QAW039 due to a very slow off-rate from the CRTh2 receptor, and a prolonged occupancy is expected to have an impact on its clinical efficacy.

Safety, tolerability, and pharmacokinetics of QAW039

Erpenbeck et al.[40] presented the results of two randomised, single-centre, double-blind, placebo-controlled studies aiming to evaluate the safety, tolerability, and pharmacokinetics of QAW039 in healthy subjects. The first study (n=16) was a single ascending dose study with an alternating cohort design in which subjects were randomised to QAW039 at different doses (10-100 mg or 30-300 mg) or to placebo. The second study (n=32) was a multiple ascending dose study in which subjects were randomised to QAW039 or placebo within four cohorts of various doses and schedules. Overall, QAW039 was safe and well tolerated across all cohorts for all doses (range: 10-500mg), both for single and multiple dosing in these two studies. The pharmacokinetic parameters showed rapid absorption, limited accumulation, and limited impact of food on exposure.

Safety, tolerability, and pharmacokinetics of QAV680

Safety, tolerability, and pharmacokinetics of QAV680 were assessed in two double-blind, placebo-controlled Phase I studies, a single-ascending dose study (n=19) and a multiple-ascending dose study (n=40) in healthy subjects.[41] The pharmacokinetic parameters of QAV680 were assessed, and demonstrated approximate dose-proportionate area under curves and C_{max}, a rapid absorption following oral administration of either single or multiple doses with a T_{max} of 0.5-3 hours and a $T_{1/2}$ of 11.5-20.4 hours. Single and multiple doses of QAV680, up to 1,000 mg twice-daily, were safe and well tolerated. No systemic accumulation was observed, nor food impact on exposure.

Clinical Evidence on QAW039 Therapy in Eosinophilic Asthma

QAW039 was evaluated in a Phase IIa, single-centre, double-blind, randomised controlled study in which 61 patients with eosinophilic severe (GINA IV and V) asthma were randomly assigned to a 12-week regimen of either QAW039 225 mg twice-daily or placebo.[42] Eosinophilic inflammation is common in asthma, and attenuation of sputum eosinophilia is strongly associated with reduced exacerbation frequency.[43] At 12 weeks, the primary endpoint, reduction of sputum eosinophils, was met: QAW039 reduced sputum eosinophils 3.5-fold over placebo (95% CI: 1.7-7.0, p=0.001). Asthma-related QoL improved in those treated with QAW039 compared to placebo (0.59 points; p=0.008) with non-significant improvements in ACQ-7 in the group as a whole (0.40 points; p=0.084), which was greater in those with poor asthma control (ACQ≥1.5) at baseline (0.56 points; p=0.046). FEV_1 improved in those receiving QAW039 versus placebo (0.074L; p=0.408; pre-BD, 0.163L; p=0.022; post-BD).

Overall, QAW039 was associated with a favourable safety profile, consistent with the placebo group, with no reported serious AEs or deaths.

CONCLUSION

Asthma, and particularly severe asthma, is a chronic disease associated with a significant impact on QoL and HCRU, and for which some unmet needs remain unaddressed. Omalizumab has been on the market for >10 years for severe allergic asthma, but emerging therapies, such as monoclonal antibodies - the new high-affinity anti-IgE QGE031, mepolizumab, benralizumab, reslizumab - or the CRTh2 antagonists QAV680 and QAW039, may have the potential to provide additional clinical outcomes to patients, within acceptable safety profiles and pharmacoeconomics. Moreover, the development of predictive tools to evaluate treatment response and data collection on real-world populations will help refine the guidelines for optimal management of these diseases and help select the right drug for the right patient, which is of crucial importance in the era of 'personalised medicine'.

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NEW OPTIONS FOR OPTIMAL BRONCHODILATION IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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ABSTRACT

The European Respiratory Society (ERS) International Congress was held in Munich, Germany, on 6th-10th September 2014, and was a particularly important opportunity for leading experts to share recent developments and new clinical evidence for the management of chronic obstructive pulmonary disease (COPD). In recent years, new emerging therapies have allowed patients to benefit from improved clinical outcomes and quality of life, with acceptable toxicities. The 2014 guidelines of the Global Initiative for Chronic Obstructive Lung Disease identified symptom reduction as the main goal of moderate-to-severe COPD management. Combined bronchodilation therapy with different therapeutic classes was recommended as a strategy to ensure improved symptom control while containing adverse events, as opposed to monotherapy. Moreover, combination inhaled bronchodilators that are administered once-daily can improve compliance, compared to twice-daily modalities. This review will summarise newly presented clinical data at ERS 2014, providing further information on the efficacy and safety of such combinations, clinical evidence regarding COPD presentation in various populations, strategies for optimal drug delivery, and safety profile monitoring for recent therapeutic options.

Keywords: Chronic obstructive pulmonary disease (COPD), QVA149, indacaterol maleate, glycopyrronium bromide, congress highlights.

INTRODUCTION

The European Respiratory Society (ERS) International Congress was held in Munich, Germany, on 6th-10th September 2014, and was a particularly important opportunity for leading experts to share recent developments and new clinical evidence for the management of chronic obstructive pulmonary disease (COPD). COPD, a chronic and potentially life-threatening disease, affects more than 210 million people worldwide[1] and is characterised by progressive reduction in lung function, resulting in dyspnoea and significant impairment of quality of life (QoL).[1-4] Dyspnoea is the main symptom prompting patients to seek treatment, while the prevention of exacerbations is one of the most crucial objectives of COPD management.[5,6] As a result, both parameters are key objectives of newly-developed drugs and were the main endpoints of newly published clinical trial results, presented at ERS 2014, that demonstrated substantial improvements.

The 2014 guidelines of the Global Initiative for Chronic Obstructive Lung Disease (GOLD)[7] identified symptom reduction as the main goal of moderate-to-severe COPD management. Combined bronchodilation therapy with different therapeutic classes was recommended as a strategy to ensure improved symptom control while containing adverse events (AEs), as opposed to monotherapy. Long-acting bronchodilators are crucial to COPD management and can provide patients with improved and sustained lung function. This review will summarise newly presented clinical data at ERS 2014, providing further information on the efficacy and safety of such combinations, clinical evidence regarding COPD presentation in various populations, strategies for optimal drug delivery, and safety profile monitoring for recent therapeutic options.

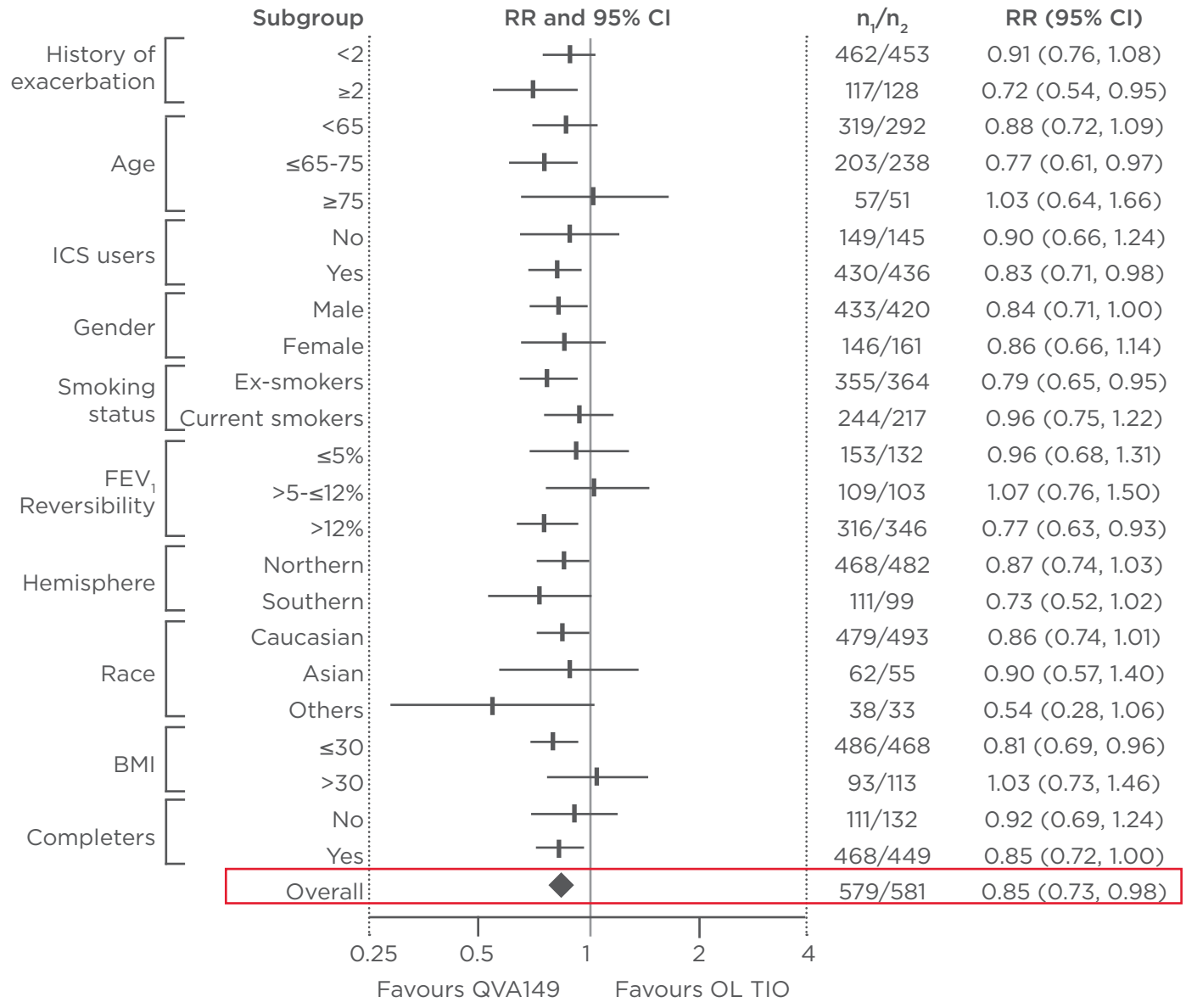

Figure 1: Overall rate ratio favours QVA149 when compared to open-label tiotropium in the majority of subgroups.

BMI: body mass index; CI: confidence interval; FEV_1: forced expiratory volume in 1 second; ICS: inhaled corticosteroid; n_1/n_2: number of patients in QVA149 arm/number of patients in OL tiotropium arm; OL: open-label; TIO: tiotropium; RR: rate ratio.

Adapted from Wedzicha JA et al.[9]

NEW CLINICAL EVIDENCE ON QVA149 (INDACATEROL MALEATE/ GLYCOPYRRONIUM BROMIDE)

QVA149 (Ultibro®, Novartis, Basel, Switzerland) is a once-daily (OD) long-acting inhaled bronchodilator used within the low resistance Breezhaler® device, and comprises the combination of indacaterol maleate (IND, a long-acting β_2-agonist [LABA]) and glycopyrronium bromide (GLY, a long-acting muscarinic antagonist [LAMA])It is already approved in over 30 countries for COPD maintenance therapy.

New Clinical Data on the Risk of COPD Exacerbations

The LANTERN study

In the 26-week, multicentre, randomised, double-blind, double-dummy, parallel-group Phase III LANTERN study,[8] QVA149 was evaluated against salmeterol (SAL)/fluticasone (FLU) in terms of

improvement in lung function, dyspnoea, health status, and exacerbations in patients (n=744) with moderate-to-severe COPD (with a history of zero or one exacerbation in the last 12 months). QVA149 met the primary endpoint of lung function non-inferiority to SAL/FLU, followed by statistically significant superiority in post-dose trough forced expiratory volume in 1 second (FEV_1) after 26 weeks of treatment (p<0.001). Moreover, QVA149 demonstrated superiority with respect to the annualised rate of moderate-to-severe exacerbations with a 31% reduction, as compared to SAL/FLU (p=0.048).

The SPARK study

The SPARK study[9] was a 64-week multicentre, randomised, double-blind, active-control, parallel-group study that aimed to evaluate the efficacy and safety of QVA149 treatment on COPD exacerbations, versus GLY and tiotropium (TIO). Patients (n=2,224) with severe or very severe COPD (GOLD Stage 3 or 4) were randomly (1:1:1) assigned to QVA149 110/50 µg, GLY 50 µg, or TIO 18 µg. Earlier results, as published by Wedzicha et al.,[2] established superiority of QVA149 over GLY, with a 12% reduction of the annualised rate of moderate-to-severe exacerbations versus GLY (p=0.038); the safety profiles for the three treatment arms were comparable. In a post-hoc analysis presented by Wedzicha et al.,[9] the rate ratio of exacerbations in severe COPD patients was analysed. The risk of moderate-to-severe exacerbation was 11% and 15% lower with QVA149, as compared with GLY (rate ratio, 0.89; 95% CI, 0.77, 1.04) and TIO (rate ratio, 0.85; 95% CI, 0.73, 0.98), respectively. Similar results were obtained across a majority of subgroups (Figure 1). No significant differences in safety profiles were observed across the three treatment arms.

New Clinical Data on Lung Function/Dyspnoea Management

The QUANTIFY Study

The QUANTIFY study[10] was a double-blind, triple-dummy study which aimed to compare the clinical outcomes of QVA149 treatment with a free-dose combination of TIO + formoterol (FOR) in patients with moderate-to-severe COPD, as evaluated by health-related QoL (St. George's Respiratory Questionnaire-COPD [(SGRQ)-C]), lung function (FEV_1, forced vital capacity [FVC]), and dyspnoea (transition dyspnoea index [TDI] responder rate). Patients (n=934) were 1:1 randomised to either QVA149 110/50 µg OD or TIO 18µg OD + FOR 12µg twice-daily. At 26 weeks, QVA149 demonstrated statistically significant improvements in lung function (FEV_1 and FVC p<0.001 and p<0.001, respectively; Figure 2), significant improvements in dyspnoea (p<0.05), and non-inferiority in terms of QoL over the standard-of-care combination of TIO+FOR. No differences in safety profiles were observed between both treatment arms.

The BLAZE study

The BLAZE study[11] was a multicentre, randomised, blinded, double-dummy, placebo-controlled, three-period crossover study which evaluated the clinical outcomes and safety of QVA149 versus TIO and placebo in moderate-to-severe COPD. Study design included six treatment sequences comprising three active treatment phases (QVA, TIO, or placebo) for 42 days, separated by 14-day washout phases. All the patients (n=247) received the three treatment options, but with different sequential orders. Previously published results demonstrated significant improvements with QVA149 regarding dyspnoea, lung function, and reduced rescue medication over TIO and placebo, as early as 6 weeks into therapy.[12] D'Urzo et al.[11] reported the outcomes for a subpopulation of patients (n=82) who received LABA and inhaled corticosteroids (ICS) prior to the study, which is highly interesting because this therapeutic strategy is not recommended by current 2014 GOLD guidelines.[7]

At 6 weeks, QVA significantly improved dyspnoea in a greater proportion of patients compared to TIO and placebo (p<0.05 for both comparisons), as evaluated by the proportion of patients achieving minimum clinically important difference (an assessment used to identify responders in clinical trials)[13] in self-administered computerised-total dyspnoea index (SAC-TDI) total score (Figure 3). Similar outcomes were observed in terms of rapid and sustained bronchodilation at day 1 and after 6 weeks, with statistically significant improvements in lung function (FEV_1). Rescue medication use was significantly reduced with QVA149 compared to placebo (QVA149 versus TIO, not significant). Safety parameters and AE occurrences as evaluated between QVA149 and TIO were similar, and the treatments were well tolerated. Similarly, a post-hoc subgroup analysis from the same study was also presented at ERS 2014, and focused on patients receiving LAMA as prior medication.[14] QVA149 was also associated,

versus placebo or TIO, with significantly improved dyspnoea (SAC-TDI, p<0.001), lung function (FEV_1 p<0.001), and reduction of rescue medication (daily puffs p<0.01).

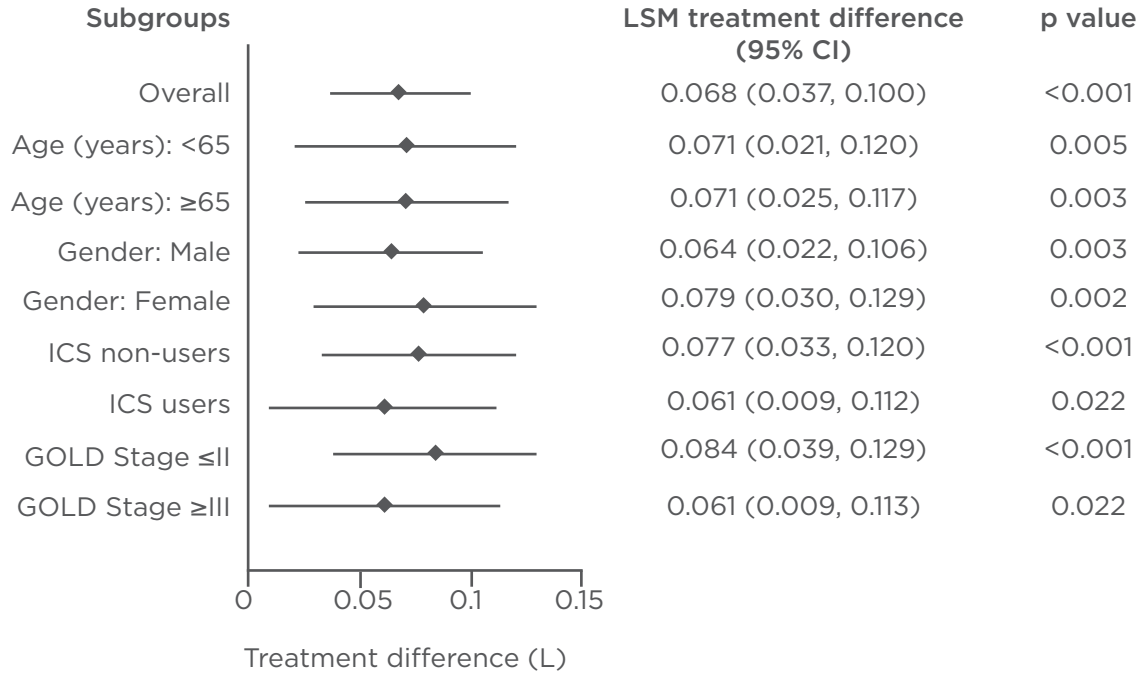

Figure 2: Forest plot of pre-dose FEV_1 at Week 26 (LOCF) by subgroups (QVA149 versus TIO+FOR).
ICS: inhaled corticosteroids; LOCF: last observation carried forward; LSM: least squares mean; TIO+FOR: tiotropium plus formoterol.
Adapted from Gessner C et al.[10]

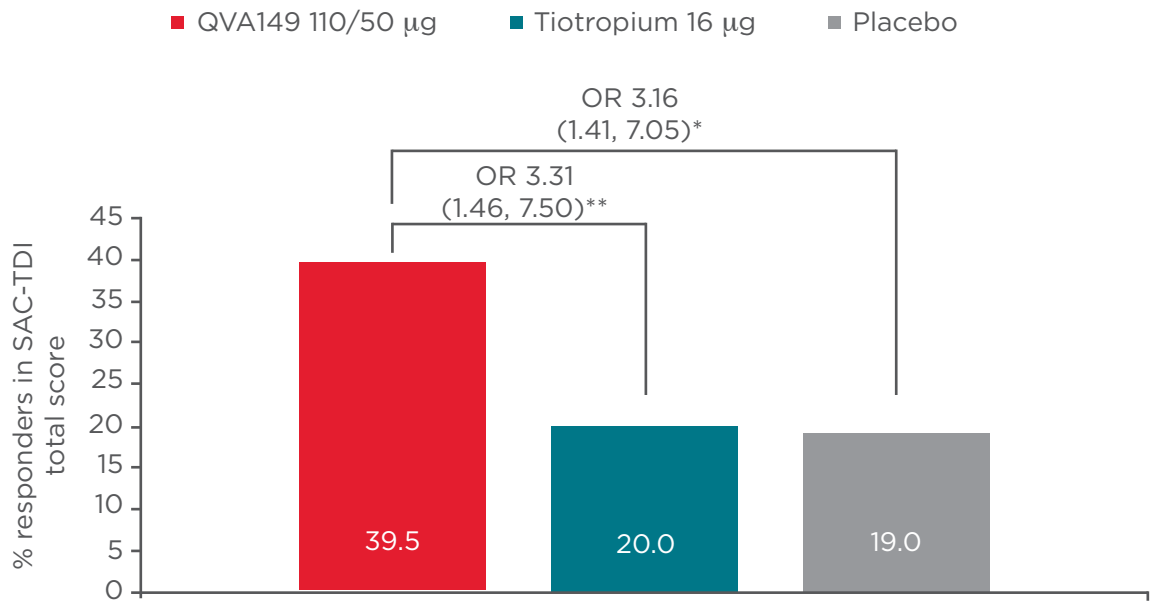

Figure 3: Percentage of responders in SAC-TDI total score in patients using prior LABA/ICS medication after 6 weeks of treatment.
*p=0.005; **p=0.004
SAC-TDI: self-administered computerised version of transition dyspnoea index; LABA: long-acting β_2-agonist; ICS: inhaled corticosteroids; OR: odds ratio.
Adapted from D'Urzo A et al.[11]

New Preclinical Data on Drug Delivery with the Breezhaler® Device

For many inhalation devices, establishing the dose-response relationship for consistent and reliable lung delivery is hindered by inter-individual variability, physiological and inspiration parameters, lack of reliable correlation between plasma levels, and efficacy quantification, as well as the small statistical power of available measurements and methods. The Breezhaler® device is a low-resistance device that can provide optimal drug deposition and reliable dose control, which is of importance as patient-related factors such as poor handling and inhalation technique may result in suboptimal drug delivery to the lower airway.[15-17]

As such, Kuttler et al.[18] reported the results of a drug-delivery modelisation study on the Breezhaler® device, aiming to determine optimal lung deposition parameters for QVA149 among variable simulated flow rates, and particle sizes in a mouth-throat model. Measurements in flow profile and turbulences aimed to evaluate the regions for greater drug loss according to the variable parameters. The results demonstrated a correlation between particle size and deposition in bronchial tissue, as well as an increased loss of drug in the mouth-throat region at a high flow rate, and a greater drug loss in the capsule/device at lower flow rates, suggesting a constant delivery of QVA149 to lung tissue across the flow rates via the Breezhaler® device. Moreover, higher drug losses were observed when GLY or IND were administered as monotherapy through the same device, in comparison with QVA149, indicating improved and optimised delivery with the fixed-dose combination.

NEW CLINICAL EVIDENCE ON GLY

GLY (Seebri®, Novartis) is an already approved OD LAMA used within the low-resistance Breezhaler® device for COPD maintenance therapy.

New Clinical Data on Lung Function/Dyspnoea Management: the GLOW6 study

As stated above, current GOLD guidelines[7] recommend the combination of different therapeutic classes (LABAs, LAMAs, and ICS) in dual or triple therapy to ensure optimal management of COPD patients and improved clinical outcomes with similar safety profiles, as compared with monotherapy. Nevertheless, to date, clinical data on triple combination strategies remain scarce.[19] The GLOW6 study[20] was a 12-week, multicentre, randomised, double-blind, parallel-group, placebo-controlled study aiming to compare the efficacy and safety of GLY+IND combination therapy versus IND monotherapy in moderate-to-severe patients (n=449), and for which the results were previously published.[21] In a post-hoc analysis (n=280), Vincken et al.[21] presented the efficacy and safety results of free-dose triple combination (GLY + IND + ICS) versus free-dose double combination (IND + ICS) therapy. The triple combination yielded significantly higher improvements in lung function (as assessed by FEV_1, as early as day 1, p=0.012) and dyspnoea at 12 weeks (p=0.041) versus the double combination. The safety profiles of both regimens were comparable with no clinically meaningful differences.

New Clinical Data on Lung Function and Health Status: the GLISTEN study

Frith et al.[22] presented the results of the GLISTEN study, a multicentre, randomised, blinded, double-dummy placebo and active-controlled, 3-arm parallel group, 12-week trial aiming to assess non-inferiority of inpatients with COPD already receiving the ICS/LABA FLU/SAL. The study met its primary endpoint as the GLY combination with FLU/SAL demonstrated non-inferiority to TIO+FLU/SAL in terms of trough FEV_1 at 12 weeks. The former combination also demonstrated superiority over FLU/SAL alone, as demonstrated by statistically and clinically significant improvements in trough FEV_1 at week 12 (p<0.001). Overall, the safety profile of all three arms was acceptable and consistent among treatment subgroups.

Post-marketing Surveillance Data

In an innovative analysis of post-market surveillance reports with the EMPIRICA™ Signal System (Oracle Health Sciences) data mining tool, Di Giovanni et al.[23] evaluated the safety profile of GLY since its launch in September 2012 through to March 2014. The EMPIRICA tool was used to detect and calculate any disproportionate statistic for AEs, using the multi-item Gamma Poisson Shrinker algorithm. In parallel, a traditional approach was used in the form of evaluation of individual case safety reports, scientific literature, spontaneous reports, competent authorities, non-interventional studies, and compassionate use programmes. The analyses through both approaches

revealed a consistent safety profile with regards to the approved label, particularly with regards to cardiovascular AEs and serious AEs. No new safety hazard was detected.

NEW CLINICAL EVIDENCE ON TIO + OLODATEROL COMBINATION

Data from the TONADO studies - two 52-week, double-blind, parallel-group studies - were presented at ERS 2014, and evaluated the efficacy and safety of the combination of TIO + olodaterol (a LABA) in a single inhaler (Respimat® Inhaler, Boehringer Ingelheim) versus TIO or olodaterol alone in 5,162 patients with COPD.[24] At 24 weeks, the combination was superior ($p<0.001$) to monotherapy with either TIO or olodaterol in terms of lung function (trough FEV_1 response) and QoL (SGRQ), these improvements being clinically relevant.[24] Overall, the safety profile of the combination was consistent with those of TIO or olodaterol therapy alone.[25]

DEFINING AND IDENTIFYING NEW STRATEGIES

Stepwise Withdrawal of ICS and Lung Function

The WISDOM study,[26-28] a 12-month, double-blind, parallel-group, active-controlled study, aimed to evaluate the impact of stepwise withdrawal of ICS on lung function in GOLD 3/4 COPD patients (n=2,485) receiving the combination of TIO, SAL, and FLU. After 6 weeks, patients were randomised to either continue therapy or to undergo stepwise withdrawal of ICS over 12 weeks (dose reduction every 6 weeks). ICS withdrawal was non-inferior to ICS use in lung function, as assessed by trough FEV_1, at both 18 and 52 weeks ($p>0.0001$ and $p<0.01$, respectively) and in the risk of moderate-to-severe exacerbations. The authors explained that these results demonstrated that many patients with severe COPD may not require ICS use, despite the latter being recommended by GOLD guidelines, which is interesting in clinical practice because ICS represent a potential for an additional burden due to their related AEs.

New Clinical Evidence on Blood Eosinophil Levels and the Risk of COPD Exacerbations

Two studies explored the utility of measuring blood eosinophil levels with respect to the risk of COPD exacerbation in patients receiving ICS therapy. The findings resulted from post-hoc analyses conducted on trials evaluating Relvar® Ellipta® (GlaxoSmithKline, FLU + vilanterol, a LABA) and Anoro® Ellipta® (GlaxoSmithKline, umeclidinium [a LAMA] + vilanterol [a LABA] OD combination). The results revealed that baseline blood eosinophil count could be a biomarker of improvement of exacerbation rates in patients receiving FLU + vilanterol, the higher the eosinophil level, the greater the improvement.[29] However, a post-hoc analysis on patients who received umeclidinium and vilanterol, either as monotherapy or in combination, did not reveal any differences in terms of responsiveness to bronchodilator treatment according to the blood eosinophil count, meaning that this measurement is not a predictor of response to bronchodilator treatment.[30]

REAL-LIFE DATA ON COPD

Over recent years, several initiatives have emerged to implement registries and studies in order to collect real-life data on COPD presentation in the general population, as well as treatment pathways and prescription behaviours. Indeed, obtaining data reflective of real-world populations as opposed to clinical trial populations is very important to help refine management guidelines and identify patients likely to respond better to select therapies.

COPD Distribution and Disease Characteristics in a German population

The DACCORD study[31] was a national, prospective observational cohort study initiated in Germany across 349 centres, collecting data from 6,208 patients with COPD, with an enrolment based on GLY medication (2:1). The main objective was to evaluate the distribution of COPD patients among all four GOLD 2011 categories (ABCD groups, assessing both lung function and symptoms and risks of experiencing exacerbations).[32] A wide range of clinical and therapeutic parameters were recorded, including spirometry, history of exacerbations, COPD assessment test (CAT), Modified Medical Research Council Dyspnoea Scale, comorbidities, smoking history, and long-term oxygen use.

Preliminary results revealed that the majority of patients had mild (17.8%) to moderate (48.5%) disease (GOLD 2010 criteria),[33] with 50.4% of patients being classified in C and D categories (GOLD 2011 criteria)[32] according to lung function and exacerbation history. In the 6-month period prior to enrolment, 27.6% of patients experienced

COPD exacerbations, with 7.8% of patients suffering from two or more episodes.[34] Higher CAT score (>30) was associated with a high exacerbation frequency (48.6%), as compared with CAT score <10 (16.2%). However, no significant differences were observed regarding GLY use or age distribution. The study will span over the next 2 years, interim 1-year data being expected by early 2015.

Treatment Pathways and Prescription Patterns within a UK Population

In a global, retrospective, observational study, the prescribing patterns 1 year prior, and up to 13 years following, initial diagnosis of COPD were recorded in order to identify the main treatment pathways from diagnosis to triple therapy, predictors for prescription, and the rationale behind the choice of initial therapy.[35,36] The UK patient dataset results were presented at ERS, and included data from 20,154 patients from 318 practices, using the Optimum Patient Care Research Database which collects anonymous longitudinal data from >1 million UK patients. In the first analysis subset,[35] data from the 16,185 patients composing the final study population revealed that the main predictors for prescription of first therapy and first maintenance therapy for COPD were comorbid asthma, increasing exacerbation rates, and decreasing lung function.

After excluding patients with comorbid asthma, the analysis revealed that the prescribing patterns were not consistent with GOLD first and second choice recommended therapies according to GOLD category. Long-acting bronchodilator monotherapies were underused, particularly in GOLD A and B categories in which ICS regimens were prescribed (33 and 36% of patients, respectively), despite not being recommended. Overall, ICS monotherapy was prescribed across all four GOLD categories, despite also not being recommended (Figure 4).

Initial therapy	GOLD group, n (%)				Total n (%)
	A	B	C	D	
None	1,784 (34)	982 (31)	597 (27)	590 (26)	3,953 (31)
Short-acting agents	1,506 (29)	927 (29)	575 (26)	520 (23)	3,528 (27)
LABA	51 (1)	61 (2)	32 (1)	49 (2)	193 (2)
LAMA	149 (3)	67 (2)	76 (3)	56 (3)	348 (3)
LABA + LAMA	7 (0.1)	2 (0.1)	3 (0.1)	8 (0.4)	20 (0.2)
ICS	831 (16)	551 (17)	362 (16)	395 (17)	2,139 (17)
ICS + LABA	746 (14)	503 (16)	487 (22)	538 (24)	2,274 (18)
ICS + LAMA	43 (1)	22 (1)	27 (1)	19 (1)	111 (1)
ICS + LABA + LAMA	93 (2)	71 (2)	88 (4)	89 (4)	341 (3)
Other	4 (0.1)	5 (0.2)	0 (0)	6 (0.3)	15 (0.1)
Total n (%)	5,214 (100)	3,191 (100)	2,247 (100)	2,270 (100)	12,922 (100)
First choice therapy	29%	4%	23%	42%	
First or second choice therapy	33%	4%	23%	43%	
Not on recommended therapy by GOLD 2013	67%	96%	77%	58%	

GOLD first choice therapy GOLD second choice therapy

Figure 4: Initial therapy by GOLD Group for non-asthma patients only.
LABA: long-acting β_2-agonist; LAMA: long-acting muscarinic antagonist; ICS: inhaled corticosteroids; GOLD: Global Initiative for Chronic Obstructive Lung Disease.
Adapted from Price D et al.[35]

In another subset,[36] the results from 11,858 patients without comorbid asthma showed that about 29% of patients received triple combination therapy after initial diagnosis. The majority of patients who progressed to triple combination therapy did so within 3 years of initial diagnosis; the GOLD category did not have an impact to progression to triple therapy.

Disease, Patients, and Treatment-Related Parameters in an Italian Population

The methodology[37] and preliminary results[38] of the 3-year MISTRAL study - an Italian, observational, longitudinal, prospective multicentre trial - were presented at ERS 2014. The aim of this study was to describe the therapeutic approaches and COPD management evolution as defined by the GOLD guidelines, in both patients with frequent and non-frequent exacerbations.[32] Indeed, the identification of patients more likely to respond to therapy is a crucial objective and recent findings indicate that adherence to GOLD guidelines is low,[39] warranting a large-scale, real-life study tailored to acquire treatment pathway prescription trends and prognostic factors and parameters.

With an enrolment target of 1,500 patients within 72 centres, this study involves 1 enrolment visit and 6 follow-up visits every 6 months. Patient characteristics, clinical outcomes, patient-related parameters, and treatment-related parameters were documented. Preliminary results were presented on the female subpopulation, which is of particular interest as recent reports suggest that women could be at higher risk of COPD and may present more invalidating symptoms and COPD exacerbations than men.[40-43] Between the two cohorts, women represented 21-24% of the subjects (men/women ratio, 3.5:1). Data from the first 139 women suggested that this subpopulation is younger, with a younger age at diagnosis, and presents shorter disease duration. However, a comparison of the female versus male cohorts revealed that a higher percentage of women were smoking at the time of the study.

CONCLUSION

In recent years, new emerging therapies have achieved improved clinical outcomes and QoL with acceptable toxicities. Combination inhaled bronchodilators that are administered OD can improve compliance compared to twice-daily modalities. Nevertheless, some unmet needs are yet to be addressed, and COPD remains a disease associated with a high burden. Registries and observational studies will certainly help to identify patient subsets most likely to benefit from select therapies, as well as help to refine management guidelines.

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EVENT-DRIVEN STUDIES AND SERIOUS CHRONIC DISEASES: ADDRESSING PLACEBO, DRUG EFFICACY, AND TREATMENT FAILURE IN PULMONARY ARTERY HYPERTENSION

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ABSTRACT

Clinical development of novel therapies for pulmonary artery hypertension (PAH) requires trials of larger patient cohorts, who are studied for longer periods and with more robust and meaningful efficacy endpoints, using event-driven studies. When employing an event-driven methodology in orphan conditions such as PAH, it is important to consider study endpoints, the use of placebo, and the approach used for treatment. The most relevant clinical endpoints in rare conditions, such as death, can be a rare event in the trial duration. The use of composite or surrogate endpoints based on biomarkers can provide a wealth of information regarding benefits observed in randomised controlled trials (RCTs). Biomarkers that predict morbidity and mortality at an early stage are required. The use of placebo in event-driven studies of PAH is a growing issue, as the development of novel treatments over past years means that future therapies possibly cannot be compared against placebo. Crossover study designs, randomised discontinuation trials, registry trials, and re-randomisation may instead be utilised in RCTs of PAH. Owing to the heterogeneity of responses to PAH treatment, differing strategic approaches should be assessed in RCTs including combination therapy and sequential therapy.

Keywords: Event-driven study, pulmonary artery hypertension, study endpoints, biomarkers, composite endpoint, surrogate endpoint, combination therapy, sequential therapy.

INTRODUCTION

Chronic disease affects almost every aspect of a patient's life; ranging from physical and mental health, to their ability to function day-to-day both as an individual, and on a societal level. Studies of chronic diseases must be sufficiently powered to assess the effects of treatment on all clinically-relevant aspects of the disease, while including appropriate endpoints to directly measure how the patient feels, functions, or survives.[1]

In some serious, rare conditions this is compounded by a small patient population and a general lack of consensus on the best endpoints. For example, pulmonary artery hypertension (PAH) is a progressive orphan disease occurring in 15 people per million adults per year.[2] As a result, randomised clinical studies (RCTs) of PAH have traditionally been of short duration, comprised small populations of affected patients, and limited in evaluating the scope and duration of treatment effects. Clinical development of novel therapies for PAH in the future will require trials of larger patient

cohorts who are studied for longer periods, and with more robust and meaningful efficacy endpoints.[1] One approach is to use registry-based or open-label studies to generate patient-level data. But, while national registries and open-label studies give an indication of population survival, there are limitations that need to be considered when extrapolating to the individual patient. As they include unselected, 'real-world' patients, registries comprise mixed patient populations with different comorbidities and co-medications. The applicability of data from mixed patient populations to the individual is therefore unclear.[3]

There is currently interest in the use of event-driven, or outcome-driven, studies for investigating patient-level responses in serious, rare diseases. Event-driven studies are less dependent than traditional RCTs on achieving pre-specified sample size, instead being powered to detect the occurrence or frequency of predefined events. Traditional sample size criteria are often employed to assess the number of events required to fulfil the hypothesis-testing approach. Such an approach enables the true clinical progression of serious, rare conditions to be assessed over time.[1] In all RCTs, the calculation of sample size is based on the anticipated number of events – estimated using previously published data – and the number of subjects enrolled is estimated in order to obtain the required number of events with adequate follow-up, including losses to follow-up or drop-out.[4]

When employing an event-driven methodology in orphan conditions such as PAH, it is important to consider study endpoints, the use of placebo, and the approach used for treatment.

ENDPOINTS AND METHODOLOGY OF EVENT-DRIVEN STUDIES

A study endpoint may be defined as the occurrence of a clinical sign, symptom, or change in parameters that is predefined as a target outcome of the study. A primary endpoint is the outcome that defines the success or failure of the treatment under investigation. Secondary endpoints, in contrast, are investigated but meeting these endpoints is not critical to the success or failure of the study. In order to provide an understanding of survival and event-free survival in patients with serious, rare diseases, as well as to evaluate the efficacy of drugs and treatment strategies on long-term outcomes and prognosis, event-driven studies require appropriate endpoints.[5] In general, endpoints should be well defined, reliable, sensitive to the effects of the interventions, readily measureable and interpretable, and clinically meaningful. The strongest endpoints are outcomes that are direct measures of clinically meaningful benefits to patients.[1,5]

The most relevant clinical endpoints can be relatively rare. In PAH there is a need to evaluate the efficacy of drugs and treatment strategies on long-term morbidity and mortality outcomes in order to truly determine the effect of treatment on prognosis. But, as death, for example, is a relatively rare event, to conduct a mortality study in serious, rare diseases with enough statistical power to detect a treatment effect, a large number of patients would be required. In addition, it is generally perceived that when multiple therapies are available, conducting a survival trial would be unethical. The use of composite endpoints as a primary outcome requires that the trial is event-driven, or outcome-driven, rather than being of a fixed observation time.[5]

Event-driven studies tend to focus on longer duration primary outcomes – such as time to treatment discontinuation, all-cause mortality, and time to death or hospitalisation[6-9] – which may not be appropriate effectiveness measures for acute illnesses, where healing may occur within a short time, or in intermediate illnesses in which symptoms come and go.[6] In order to gain more information regarding the patient's condition, more descriptive secondary outcomes may also be employed, such as disease-specific changes (e.g. oedema, body weight, dyspnoea) or rates of adverse events during the treatment phase.[6-9]

The use of surrogate endpoints can provide a wealth of information regarding the mechanism of action of benefits observed in RCTs. For example, in studies of systemic hypertension, blood pressure reduction is a frequently used endpoint because it has been shown to be a surrogate for survival.[10] In PAH, changes in pulmonary haemodynamic parameters during the typical period of a RCT (i.e. at 16 weeks) is useful to determine long-term prognosis.[11] Such endpoints may be particularly useful in RCTs, and the clinical management, of orphan diseases such as PAH. Indirect surrogate endpoints that are commonly used in PAH include the 6 minute walking distance (6MWD), cardiopulmonary haemodynamics, and biomarkers.[12] It is worth

noting that some indirect surrogate endpoints are dependent on patient motivation or clinical judgement. To eliminate this, there may be a preference for surrogate markers that measure biological processes: namely biomarkers.[5]

In RCTs and the clinical management of PAH, there is a need for biomarkers that identify the disease and are able to predict morbidity and mortality at an early stage.[13] Levels of brain natriuretic peptide (BNP) and the N-terminal fragment of pro-BNP have been identified as biomarkers for mortality risk stratification, but there is no established threshold for good or poor prognosis.[12] Also, despite the observation that patients who respond to treatment with short-acting vasodilators are likely to respond to treatment with calcium channel blockers, treatment responses in PAH are generally unpredictable and additional biomarkers are required to assess this.[12] Biomarkers can also be used to assess the effects of treatment and any change in a biomarker as a result of an intervention is considered direct evidence of biological activity. It is important to bear in mind, however, that such evidence can be unreliable. This is particularly the case if biomarkers are strongly correlated with clinical efficacy measures in natural history observations, yet are not in the causal pathway of the disease process.[5]

Completed and ongoing studies in PAH have utilised composite endpoints to enable a stringent assessment of the effects of treatment on clinically-relevant outcomes. The Phase III SERAPHIN study,[14] for example, assessed the efficacy of macitentan using a primary endpoint that was a composite of death, atrial septostomy, lung transplantation, initiation of treatment with intravenous or subcutaneous prostanoids, and worsening of PAH. SERAPHIN also utilised a rigorous definition of PAH worsening to define morbidity and mortality. In this study, PAH worsening was defined as a decrease in 6MWD by 15%, confirmed by a second test, worsening of PAH symptoms, and the need for additional PAH treatments. The mean duration of study treatment was up to 103.9 weeks.[14] Based on data from SERAPHIN, macitentan is recommended to delay the time to clinical worsening in treatment-naïve PAH patients and in patients with symptomatic PAH despite treatment with a phosphodiesterase Type 5 inhibitor.[12]

The Phase III GRIPHON study[15] is an ongoing investigation of selexipag versus placebo in patients with PAH. The primary endpoint is the time to first morbidity or mortality event, over a period of up to 4.3 years; which is defined as death or hospitalisation for worsening of PAH, resulting in need for lung transplantation or balloon atrial septostomy, initiation of parenteral prostanoid therapy or chronic oxygen therapy, or disease progression.[15] The AMBITION study[16] is an ongoing Phase III assessment of first-line ambrisentan combined with tadalafil versus monotherapy with ambrisentan or tadalafil for PAH. The primary endpoint is time to clinical failure, with an estimated study duration of 3.5 years. Secondary endpoints include change from baseline in 6MWD, change from baseline in N-terminal pro-BNP, and proportion of patients with unsatisfactory clinical response.[16]

Therefore, event-driven studies – such as SERAPHIN,[14] GRIPHON,[15] and AMBITION[16] – are not only key in driving the future of therapy in PAH, these trials also have an integral role in defining the endpoints and characteristics of future studies. SERAPHIN,[14] for example, demonstrates that large-scale, long-term studies on morbidity and mortality in PAH are feasible. GRIPHON[15] and AMBITION[16] should provide data regarding appropriate primary and secondary outcomes and the timing of these outcomes, thus guiding the selection of endpoints and the duration of future studies.

ISSUES IN PLACEBO-CONTROLLED EVENT-DRIVEN STUDIES (PCEDS)

PCEDS typically take the form of two distinct methodologies. In the first, the placebo or active treatment under investigation is added to the standard of care (SOC) in a single-blinded manner. In the second, only the placebo or active drug are randomised, with no SOC included; the patients included in the study receive either no therapy or the test drug. The majority of PCEDS include the addition of the active drug or placebo to a SOC.[7,8] As the SOC is recommended by clinical bodies, based on the most up-to-date efficacy and tolerability data, patients in the placebo arm should, in effect, be receiving treatment with the most effective agent or combination of agents.

PCEDS studies cannot be ethically performed in illnesses where a SOC or multiple therapies exist. As per the Declaration of Helsinki: "Every patient—including those of a control group, if any—should be assured of the best proven diagnostic

and therapeutic methods."[17] It is also the case that in clinical practice, a patient diagnosed with PAH would always receive active treatment. Hence, when an active treatment exists, the control arm should not receive placebo without SOC as this is unethical and methodologically incorrect. This is the case in PAH, where the development of novel treatments over past years means that future therapies cannot be compared against placebo.[1] Yet there is a clear need for the development and investigation of novel efficacious treatments for PAH. Novel clinical trial designs are therefore required.

Crossover designs may be considered for PAH studies, in which subjects complete one course of therapy and are then switched to a different therapy. A crossover design is effective in assessing short-term differences in outcomes between two treatment approaches, though it utilises a short washout period and assumes negligible carry-over effects of treatment. In PAH, any washout period raises the concern of rebound of clinical symptoms.[18] Other novel approaches to study design have also been developed. Factorial trials, for example, allow the testing of more than one novel element in a single trial design.[19] In a factorial trial, participants are allocated to receive neither intervention, one or the other, or both interventions. By including all participants in both analyses, such a design enables consideration of the separate effects of each intervention, as well as the benefits of combining the interventions. However the power of factorial trials may be limited and large populations required to achieve adequate power.[19]

Randomised discontinuation trials (RDTs) are a second novel study design. RDTs are two-phase studies, in which all participants are treated open-label with the investigational drug in Phase I. Those who respond to treatment enter Phase II and are randomised to placebo or to continue treatment. This approach eliminates non-compliers and adverse reactions.[20] In one analysis, the RDT methodology was found to have a very strong effect on trial efficiency and required a sample size 20–50% that of a traditional RCT.[20] There is concern that removal of the active drug in Phase II of RDTs may be detrimental to participants. Also, the selected population may not be representative of the larger affected population.[1]

In order to strike a balance between effective treatment and data generation, a re-randomisation approach has also been developed. Such an approach ensures that patients are continually receiving an active treatment and can be followed for the entire study duration. Such a methodology was employed in the Clinical Anti-psychotic Trials of Intervention Effectiveness studies[6] in schizophrenic patients. In this methodology, patients were randomised to one of several medications; upon treatment failure or discontinuation, patients were re-randomised to another double-blind treatment. This treatment was discontinued at the discretion of the investigators and the subject entered into a non-randomised open-label phase. In order to further mimic usual patient care, inclusion and exclusion criteria were open, and physicians could change the dosage of the double-blind treatment whenever warranted.[6]

STRATEGIES FOR THE MANAGEMENT OF SERIOUS, RARE DISEASES INCLUDING PAH

Patients diagnosed with PAH share numerous disease-specific clinical characteristics. There are, however, numerous underlying disease processes and risk factors that can cause PAH. Particularly in the case of idiopathic PAH, disease may be caused by numerous pathological processes. Thus, RCTs generally recruit patients with PAH caused by numerous factors, which results in the heterogeneity of responses to treatment.[12] It is, therefore, essential that differing strategic approaches to treatment are assessed in RCTs.

Combination Therapy

Through event-driven studies – as described above – two strategies have emerged as being effective for the management of serious, rare diseases: combination therapy and sequential therapy. In the combination approach, one drug is administered and a second drug is added to the regimen if the patient begins to deteriorate, does not reach treatment goals, or does not improve at all. This differs from adjuvant therapy, where an additional drug(s) is added at a fixed point in the treatment pathway, such as in cancer therapy.[21]

Combination therapy is limited by the requirement for the demonstration of synergy and favourable pharmacodynamic characteristics between two or more agents.[21] In many cases, the proposed benefits of combination therapy are based on *in vitro* tests demonstrating 'synergy'. However, the demonstration of synergy varies across studies and results differ

with the methodology used. Importantly, *in vitro* phenomena should translate into clinical benefit for patients, as demonstrated in prospective RCTs.[21] Unfortunately, numerous obstacles have prevented the development of properly controlled trials of combination therapy, including the cost of multiple drug regimens and the difficulty in achieving collaboration between different manufactures on studies that examine the efficacy of one agent versus a combination of other agents.[22]

In PAH, treatment with combination therapy with two or more agents is common, owing to the numerous pulmonary vascular abnormalities that have been identified as being pathogenic. A growing number of RCTs have subsequently demonstrated the efficacy of adding a second medication to stable background monotherapy, as compared with the addition of placebo.[12] In patients with PAH who remain symptomatic despite initial therapy, it is recommended that physicians add a second agent to the patient's background therapy.[23] The aim of combination therapy should be to improve surrogate outcome measures – such as 6MWD, cardiopulmonary haemodynamics, and biomarkers – and delay the time to clinical worsening.[12] But, as different patients are likely to have different pathogenic mechanisms as the cause of their disease, the first medication will only identify patients who are responsive to that therapy.[22]

Sequential Therapy

The second strategy for treating serious, rare diseases is to switch the patient onto another drug at the point of treatment failure and discontinue the original agent. Such an approach is commonly used during treatment with antibiotics where, if an antibiotic is prescribed to eradicate an infection and the ensuing response is judged to be unsatisfactory, the physician switches to another antibiotic in the hope of achieving a better outcome. Such 'sequential' administration of treatments also occurs in clinical psychiatry. Sequential therapy may involve switches to different types of drugs, as is often the case in drug-refractory depression.[24]

New Approaches in the Therapy of Serious, Rare Diseases

Sequential therapy offers patients more than just another treatment option in the case of resistance. In cancer therapy, the concept of sequential therapy is being utilised in a 're-challenge' approach. Re-challenge is used later in the treatment pathway of an agent in which resistance has previously developed.[25] A second treatment modality, termed 'cyclic treatment', stems from re-challenge.[26] In this system, a number of drugs are selected, based on their characteristics and the patient's clinical needs, and are used sequentially. Once all the drugs have been used, re-challenge with each of the drugs is undertaken.[26] Such a methodology may prove successful in other serious, rare diseases and may be incorporated into event-driven studies.

Observations from event-driven studies – in particular using re-randomisation-type methodologies – should be used to guide drug switching strategies and develop an adaptive treatment strategy (ATS). An ATS is a set of rules for adapting a treatment plan to the changing state of an individual patient, taking into account both the history of previous treatments and the response to those treatments.[27] For example, the clinical management of HIV infection may begin with a particular combination of anti-viral medications and then, as the patient's viral load and CD4 count change over time, the combination may be changed or other treatments may be instituted.[27] ATSs may be an essential component of PAH management, where individualised approaches to treatment are required, owing to the heterogeneity of responses across PAH patients.[12] Also necessary is the identification of biomarkers and genes that can predict treatment responses, and thereby facilitate an approach to therapy that is tailored to individual patients.

As medicine improves its abilities to stave off mortality, the result is a growing list of previously acute conditions that have become chronic.[27] This necessitates the introduction of new RCT methodologies and treatment approaches to study the management of serious, rare diseases, and identify novel biomarkers to predict treatment responses and prognosis.

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RATIONALE FOR ENDOBRONCHIAL COIL TREATMENT AS THE PRIMARY INTERVENTION FOR PATIENTS WITH SEVERE EMPHYSEMA

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) is a chronic, progressive, and debilitating disease, particularly in its final stages. The National Emphysema Treatment Trial demonstrated that surgical removal of diseased portions of the emphysematous lung improved clinical and functional status of a subgroup of severe patients with upper-lobe predominant emphysema and low baseline exercise tolerance. However, questions about morbidity, mortality, and costs have all fuelled growing enthusiasm for endoscopic methods of achieving improved clinical outcomes in this poorly-served patient population. Among the various available methods, endobronchial coil therapy is a particularly promising technique that improves exercise capacity, pulmonary function, and quality of life in severe emphysema, with an acceptable safety profile and growing clinical evidence of sustained improvement. Notably, coil treatment appears effective in broader groups of patients than can be treated with other methods or surgery. Coil treatment as the preferred method for treating severe emphysema represents a welcome paradigm shift, given the known limitations of endobronchial valves and surgery. This review addresses the clinical data available to date and proposes an alternate framework for selecting and treating patients with endobronchial coils.

Keywords: Emphysema, chronic obstructive pulmonary disease (COPD), coil therapy, bronchoscopic lung volume reduction.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a chronic, progressive, and debilitating disease, particularly in its final stages. The National Emphysema Treatment Trial (NETT)[1] demonstrated that lung volume reduction surgery (LVRS) can improve clinical and functional outcomes, as well as survival, in a subgroup of patients with heterogeneous emphysema in the upper lobes and low baseline exercise capacity. However, costs related to the surgical procedure, as well as lengthy hospital stays and recovery periods with consequent 'costs' to patients, make surgery an unwelcome option. Many LVR techniques have been developed to achieve the benefits of LVRS endoscopically. In our view, endobronchial coils represent a promising technique, based on patient benefits, broad applicability of the method within the intended population, and workflow integration to routine pulmonary practice. This review will summarise the clinical data available to date and propose a framework for selecting and treating patients with coils.

RATIONALE FOR ENDOSCOPIC TREATMENT OF EMPHYSEMA

Pathophysiology of Emphysema

Emphysema is a progressive subtype of COPD, mainly caused by smoking or environmental pollution. Emphysema is characterised by irreversible airway obstruction leading to lung hyperinflation, dyspnoea, and poor clinical outcomes. It is associated with the destruction of the collagen and fibres within the alveolar walls, consequently causing loss of elastic recoil, air trapping, and reduction of surface area for gas exchange. Hyperinflation then flattens the diaphragm, which impairs its ability to act as the main respiratory muscle, leading to dyspnoea.[2,3] The quality of life (QoL) of patients affected by this debilitating disease is severely impaired and, over time, complications can become life-threatening. Main pharmacologic and therapeutic options include bronchodilators (short/long-acting), glucocorticoids, pulmonary rehabilitation, and oxygen supplementation.[1] Other critical disease management strategies include smoking cessation, pulmonary rehabilitation, and other interventions such as nutrition counselling and mental health support. As disease severity progresses, pharmacologic management and supplemental oxygen fail to alleviate symptoms, leaving a significant population of severe patients with no viable treatment option.

Surgical and Non-Surgical LVR

The rationale for LVR is that removing the most diseased lung tissue would allow re-expansion of compressed, healthier tissue, shifting lung compliance, and restoring the mechanic function of the diaphragm.[4] Both surgical (tissue removal) and bronchoscopic (atelectasis) techniques have been proposed, with clear benefits as well as significant drawbacks. LVRS consists of the surgical removal of 20-35% of the emphysematous tissue of each upper lobe. Its clinical efficacy and safety profile were evaluated in many non-randomised studies,[1,5,12] but the largest clinical study was the multicentre, prospective, randomised, controlled NETT (n=1,218).[1] Primary endpoints were survival and maximal exercise performance at 24 months. LVRS was evaluated against maximal medical therapy, and was most effective in patients with heterogeneous, upper-lobe predominant emphysema, low exercise capacity, and low baseline perfusion to the upper lobes.[13,14] LVRS is, therefore, limited to very severe patients with a specific disease phenotype, yet able to survive high rates of morbidity, which include respiratory failure, prolonged air leak, infection, and thromboembolic events (operative mortality rate, 6%; major pulmonary morbidity, 30%; major cardiovascular morbidity, 20%).[15-19] LVRS is considerably more costly than standard medical therapy; in NETT, its 5-year cost-effectiveness was $140,000 per quality-adjusted life-year gained.[1,20]

Endoscopic LVR (ELVR)

ELVR refers to techniques delivered via a flexible fibre optic bronchoscope, typically requiring a hospital stay of just a few days. Benefits of established techniques include rapid patient recovery and similar or superior clinical improvement versus LVRS, without the morbidity and burden associated with surgery.[21]

Endobronchial/intrabronchial valves

Endobronchial valves (EBV) and intrabronchial valves are one-way valves that are designed to induce atelectasis of the most hyperinflated lobe. When properly placed to fully occlude all airways into a lobe, the one-way valves open upon exhalation, allowing air and fluid to exit the lobe, and close upon inhalation, preventing air from entering the lobe, resulting in eventual lobar collapse, compliance shift toward healthier tissue, and reduction of residual volume (RV). The randomised, controlled VENT trial[22,23] evaluated the use of EBV, in which unilateral treatment was assessed for improvement in forced expiratory volume in one second (FEV_1), dyspnoea, and QoL in 321 patients with severe heterogeneous emphysema. Only modest improvements were observed for all endpoints, resulting in FDA denial of approval.[24]

The challenges of EBV in real-world clinical practice are clear. As summarised in a recent literature review by Shah et al.,[25] and in retrospective analyses of the VENT trial, EBV cannot be used in patients with collateral ventilation (CV) - a condition highly prevalent in severe emphysema, where openings in lobar fissures allow backfilling of air into the treated lobe via the adjacent lobe.[25] The proportion of patients that respond to EBV treatment improves from 20% in the unselected population (i.e. VENT) to 75% with appropriate patient selection. Fissure analysis can be conducted via high-resolution computerised tomography (CT), using

a threshold of >90% integrity to select patients for EBV treatment.[1] In the European cohort of the VENT trial, only 33% of patients had an intact lobar fissure, indicating a need for a treatment strategy uninhibited by this condition. A major limitation of CT fissure analysis, however, is the subjective nature of visual quantification and inconsistency in assessing the degree of integrity.[26] A system to directly assess CV requires that the patient undergo a bronchoscopic procedure during which the pulmonologist will perform a visual, subjective assessment of changes in pressures and flow within the target lobe, fully occluded by a specialised balloon catheter. The system has been demonstrated to have an overall predictive value of only 75%.[27]

Baseline perfusion is another consideration for valve therapy. A retrospective analysis of the VENT trial[28] showed that heterogeneous patients with high baseline perfusion have worse exercise capacity outcomes following EBV-induced atelectasis of a contributing lobe. Therefore, baseline perfusion testing is a critical consideration for valve therapy. Finally, very recently, a National Institute for Health Research (UK) protocol was approved to evaluate EBV treatment in patients with COPD, in which patients will be excluded if they "would be unlikely to survive a pneumothorax if it occurs."[29] This relates to a known and potentially severe consequence of the valve's mechanism of action, namely, atelectasis-induced pneumothorax.

Nitinol coils

The endobronchial coil is a nitinol (nickel-titanium) shape-memory coil that is designed to mechanically increase elastic recoil in the diseased lung by gathering and compressing lung parenchyma. It is straightened for delivery into the target sub-segmental airway, deployed via a specialised catheter, and regains its three-dimensional shape as it is released, with the effect of shortening the airway and thereby increasing regional radial tension. Approximately ten coils distributed evenly throughout the target lobe appear to yield significant and sustained clinical benefit,[30] although clinical and commercial experience suggests that the larger lower lobes may require more coils.[31]

The mechanism of action of coils is unique as it does not rely on atelectasis; rather, the mechanical re-tensioning of tissue appears to improve lung mechanics as well as support radial suspension of airways, preventing airway collapse and dynamic hyperinflation. This unique mechanical function is believed to explain the significant improvements in exercise capacity seen in patients treated with coils, despite a less impressive increase in FEV_1.[32] As the coil is not a blocking device, it does not rely on the absence of CV to produce clinical improvements. Thus, a significant step in the screening process can be eliminated, saving time and expense, as well as preventing patients from undergoing an additional bronchoscopic procedure. As the coils are not shunting devices, it is believed that they do not compromise, or significantly impact perfusion within the treated lobe. Finally, because EBV is reserved for patients in a severe and therefore frail state, the comorbidities associated with any treatment must be considered. Atelectasis-induced pneumothorax rates in patients treated with valves are increasing as patient selection improves, and as pneumothorax does not always occur before hospital discharge, patients and families must be aware of the signs of pneumothorax so that prompt medical attention can be sought.

Coil treatment involves two separate procedures to treat two contralateral lobes. CT-based patient selection involves visual analysis to exclude patients with severe bullous disease, suspicious nodules, active infection, and insufficient residual parenchyma according to a 0-5 point visual scale.[33] The most visually damaged lobe on either side will be treated. The procedure takes 20-30 minutes depending on patient anatomy and physician experience. The objective of this treatment is to place approximately ten coils sub-segmentally, distributing the coils evenly throughout the lobe (Figure 1). Deployment is achieved under fluoroscopic guidance. Three coil sizes are available (100/125/150 mm) and correspond to the total length of the device. Unlike valve procedures - where sizing and placement is absolutely critical in order to avoid missed lobar occlusion, expectoration, and/or migration - success of coil treatment does not appear dependent on specific placement within the patient's anatomy, and coils do not appear to migrate/dislodge, even up to 3 years post-implantation.[34]

Other Bronchoscopic Techniques

Other ELVR techniques include biologic volume reduction with a sealant to collapse diseased tissue,[35-37] thermal airway ablation,[38,39] and airway bypass.[40] These will not be discussed in this paper as they have achieved limited success and are not currently in clinical or commercial use.

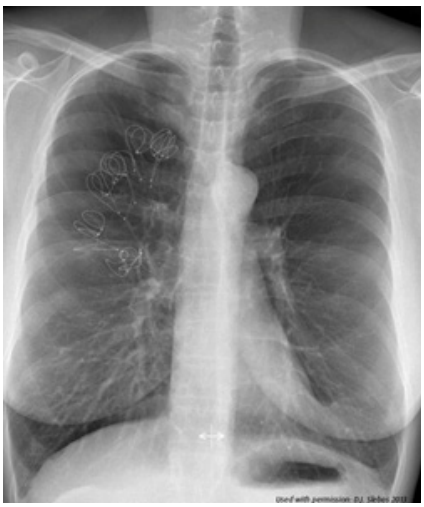

Figure 1: Sub-segmental coil placement, first treatment. Objective is to achieve even distribution of coils throughout the sub-segmental region.

LVR COIL TREATMENT

Rationale as First-Line Therapeutic Option in Severe Emphysema

As discussed above, LVRS and EBV are useful techniques that can alleviate symptoms and improve clinical outcomes. However, their applicability is limited to patients with upper lobe heterogeneous disease and low baseline perfusion, while CV (a factor for EBV) and high exercise capacity further restrict the patient pool.[25] Importantly, neither method has been proven effective in treating homogeneous emphysema, in which the disease is dispersed throughout the upper and lower lobes. As discussed below, coil treatment in homogeneous emphysema has been prospectively evaluated, and growing clinical and commercial experience demonstrates its effectiveness in the majority of severe patients who present with homogeneous disease.

Review of Data Supporting LVR Coil Treatment

To date, four clinical publications describing coil treatment of severe emphysema are available, including one published randomised, controlled trial. Two large-scale randomised, controlled trials are ongoing or awaiting publication.

Pilot studies

Slebos et al.[41] published results of a prospective cohort pilot study in 16 patients with severe heterogeneous emphysema, of whom, 12 received bilateral treatment and 4 unilateral treatment, for a median of 10 coils per patient.[41] At 6 months, QoL as assessed by St George's Respiratory Questionnaire (SGRQ; -14.9±12.1 points), FEV_1 (+14.9%±17.0%), forced vital capacity (FVC; +13.4%±12.9%), RV (-11.4%±9.0%), and exercise capacity as assessed by the 6-minute walk test (6MWT; +84.4 m±73.4 m) were all significantly ($p<0.005$) improved from baseline. Deslee et al.[30] published the results of a multicentre European feasibility study on 60 patients, of whom 55 were treated bilaterally.[30] Per protocol, 34 patients completed 12 months follow-up, demonstrating sustained benefits from treatment at 1 year (6MWT +51.4±76.1 m, $p=0.003$; SGRQ -11.1±13.3, $p<0.001$; FEV_1 +0.11±0.3 L, $p=0.037$; RV -0.71±0.81 L, $p<0.001$). Serious adverse events (SAEs) within 30 days of treatment included COPD exacerbation (n=7), pneumonia (n=6), pneumothorax (n=4), and haemoptysis (n=1). In a single-arm, open-label feasibility study, Klooster et al.[31] reported on 10 patients with strictly homogeneous emphysema and hyperinflation, receiving bilateral treatment with a median of 11 coils in each lobe.[31] Exercise capacity was improved (6MWT, 289 to 350 m, $p=0.005$), as well as the FVC (2.17 to 2.55 L, $p=0.047$), RV (5.04 to 4.44, $p=0.007$), and QoL (SGRQ, 63-48, $p=0.028$). A significant decrease in volume-dependent airway resistance was also observed after bilateral treatment, suggesting improvement in lung compliance, and supporting the mechanism of action of airway tethering. In total, 140 patients were treated in 4 European clinical studies with similar protocols and inclusion/exclusion criteria, as reported in peer reviewed publications, including one randomised, controlled study.

Randomised studies

RESET[42] was the first non-blinded, multicentre, randomised study on 47 patients with severe emphysema and severe hyperinflation.[42] Patients were 1:1 assigned either to treatment or best medical care. The primary endpoint was QoL, as evaluated by improvement in SGRQ 90 days after final treatment (approximately 6 months post-baseline). The SGRQ difference was -8.39 points in favour of the coil group. Coil treatment also improved exercise capacity (6MWT +63.55 m, $p<0.001$) and pulmonary function (RV -0.31 L; FEV_1 +10.62%). In 2012, the French Ministry of Health approved and funded a 1:1 randomised, controlled trial (REVOLENS)[43] to evaluate the clinical benefits

and cost-effectiveness of bilateral coil treatment in patients with severe emphysema.[43] The project recruited 100 patients from 10 French centres and completed enrolment in October 2013, 5 months early. Following 1-year study completion, treatment on control patients is currently ongoing under a crossover protocol; results are expected in early 2015. In 2013, enrolment commenced in an FDA-approved multicentre, 1:1 randomised pivotal clinical trial, RENEW.[33] Up to 30 centres, including 5 in Europe and 1 in Canada, will enrol 315 patients by the end of 2014. The study will evaluate safety and effectiveness of coil treatment versus standard medical care with primary endpoint of 6MWT and secondary outcomes of QoL (SGRQ) and lung function. Patients with heterogeneous and homogeneous emphysema are included; control patients are able to receive treatment via a separate FDA-approved protocol at the 1-year study exit. A European multicentre registry is also actively enrolling patients in a number of European countries, with 6-month results on 100 patients expected in 2014.[44]

Patient Selection Algorithm

Patients with severe (Gold III/IV), stable, and symptomatic emphysema should be considered for a bronchoscopic or surgical intervention. In our view, determination of the most appropriate treatment should follow a comprehensive clinical evaluation, including high-resolution CT scan and recent exercise capacity and pulmonary function tests. Our routine criteria for eligibility include severe emphysema, either heterogeneous or homogeneous, RV ≥200% predicted, and total lung capacity >100% predicted. 'Pink puffers' are excellent candidates; 'blue bloaters' are less likely to respond. Patients with severe bullous disease, known in pulmonary hypertension, prior surgical lung treatment, chronic steroid use, or carbon monoxide diffusing capacity <20% predicted are not candidates for any endoscopic or surgical treatment. It is our opinion that coil treatment should be the primary intervention for patients who meet the above criteria. The selection process for coils is far less complex, less costly, and less time-consuming than that for valves. Far more patients will qualify for coil treatment, and our experience with coils suggests that a 75-80% responder rate can be expected. When patients lack sufficient parenchymal structure for coil treatment, then they may undergo additional testing to determine if valve treatment is appropriate. In our view, this approach is more workflow-efficient, cost-effective, and prevents patients from undergoing unnecessary testing for a procedure that a majority cannot benefit from.

Commercial Experience

In 2010, the coil received Conformité Européenne mark and was made available to selected, trained centres in Germany. As clinical and commercial experience with the technology has expanded, centres in Switzerland, the Netherlands, UK, Spain, Italy, France, and Turkey have started local or regional emphysema coil treatment programmes and/or studies, with results routinely presented at key respiratory congresses. At the American Thoracic Society 2014, three centres in northern Germany reported on 49 patients treated with coils using a similar selection and treatment algorithm.[45] 62 coil procedures were completed in 49 patients. Mean 1-month follow-up data were available for 41 patients (82%). Coil treatment led to a considerable improvement of 6MWD after bilateral procedures (+119±135 m; p=0.006; n=20), after the first procedure (44±131 m; p<0.001; n=41) and the second procedure (+64±110 m; p=0.097; n=20). In the bilateral group, benefits were highly significant and sustained for at least 1-year post-treatment across three centres. Coil therapy was further explored in a retrospective analysis on 26 patients with heterogeneous emphysema and incomplete fissures at Heidelberg University.[46] Notably, these patients were only treated in one lung. Pulmonary function, as assessed by FEV_1 and 6MWT was improved at 3 months but tended to decrease at 6 months follow-up. QoL (SGRQ) was significantly improved at 3 months. These results would appear to support the superiority of bilateral coil treatment for a bilateral disease.

Patient Management Following Coil Treatment

The most frequently observed severe adverse events associated with the use of coils include COPD exacerbation, pneumonia, transient chest pain, and rarely, mild haemoptysis, with low rates of pneumothorax (5-8%) being reported in the literature.[30,46] Most adverse events, in published studies with coils, occurred within 30 days following end of treatment and were resolved with standard care; no life-threatening events such as respiratory failure occurred.[30,31,41,45-47] The bronchoscopy itself has a risk profile, established in the EASE Trial,[40] where SAEs associated with a sham bronchoscopy included COPD exacerbation (18%) and pneumothorax (0.8%) within 6 months.[40] It is

therefore important to carefully consider the risk of bronchoscopy against the intended benefit. For this reason, we do not perform repeat bronchoscopies unless absolutely indicated. Management of adverse events following coil treatment is generally feasible with standard care. We tend to follow a standard pre-treatment prophylaxis which includes oral steroids and antibiotics.

CONCLUSIONS

Coil treatment is an effective option in a majority of patients with severe emphysema for whom medical management is no longer effective. The method improves exercise capacity, QoL, and pulmonary function, while presenting a very good safety profile. It is effective in both heterogeneous and homogeneous emphysema, and does not require complex diagnostic procedures to pre-qualify patients for treatment. We recognise that coil treatment as a primary intervention for the management of severe emphysema may represent a paradigm shift. We invite our colleagues to consider that the coil's mechanical airway tethering mechanism of action is superior to the atelectasis mechanism of valves, and that the simplified patient selection algorithm for coils is far more workflow and cost-efficient, with a similar benefit to patients. We expect the randomised controlled trials in larger patient populations to validate the 'coils-first' approach as access to these endoscopic treatment methods continues to expand.

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NOVEL INSIGHTS INTO CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD): AN OVERVIEW

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) is mainly caused by smoking and presents with shortness of breath that is progressive and irreversible. It is a worldwide health problem and the fourth most common cause of chronic disability and mortality, even in developed countries. It is a complex disease in which both the airway and lung parenchyma are involved. In this review we will be mainly focusing on the airway component of the disease. We have reviewed the current literature on airway inflammation and remodelling in smoking-related COPD. It is not only the tobacco smoking which can lead to chronic inflammation, but also the persistent presence of pathogenic microorganisms in the airways. Detailed data on these in COPD are sparse. One potential mechanism contributing to small airway fibrosis/obliteration and change in extracellular matrix is epithelial mesenchymal transition (EMT). When associated with angiogenesis (so called EMT-Type-3) it may well also be the link with the development of cancer, which is closely associated with COPD, predominantly in large airways. In this paper we focused on: 1) the role of inflammation in developing COPD; 2) recent observations on structural and cellular changes which might have relevance to a major feature of COPD that is poorly understood, namely, the striking vulnerability of patients with COPD to develop lung cancer; 3) the potential role of respiratory infections in COPD.

Keywords: Chronic obstructive pulmonary disease (COPD), lung cancer, epithelial mesenchymal transition (EMT), inflammation, infections, fibrosis.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a disease state which is characterised by a (not fully reversible) airflow limitation. This is commonly progressive and is associated with noxious particles/gases causing an abnormal inflammatory response of the airways.[1] The term COPD, now widely used, was introduced into the literature in 1964.[2] Later, in the 1970s and 1980s, subphenotypes such as emphysema, chronic bronchitis, chronic obstructive bronchitis, and chronic bronchitis with emphysema were used, and recommendations and international guidelines became available on how to use these specific terms to define the disease, all of which are today lumped together as COPD.[3]

Tobacco smoking is considered as the main aetiological factor in this condition, at least in Western countries. It is a complex disease, and can have both airway and lung parenchymal components involved. The airway component may lead to chronic cough and sputum production (classically termed chronic bronchitis) but also airway narrowing with airflow obstruction, most importantly with destruction/obliteration of small airways ('destructive bronchitis', which is more of a pathological entity with physiological consequences).[4-6] Small airway narrowing is the core COPD pathology with alveolar destruction occurring subsequently in about 50%, which is the process of emphysema. Emphysema is an anatomical definition, but it is associated

with enhanced breathlessness in COPD, and physiologically gives rise to a reduced diffusing capacity (a lower oxygen absorbing capacity of the lung). It also adds to airflow obstruction by reducing the elastic recoil properties of the lung tissue, so that the driving pressure for the air to leave the alveoli is reduced.[5-7]

Inflammation

Over the past two decades the dogma that inflammation is the primary airway pathology in COPD has gained broad acceptance. Chronic inflammation in COPD has been mainly characterised as accumulation of neutrophils, macrophages, and CD8+ T cells. Inflammation is said to become worse with disease severity,[8] and in very advanced disease, lymphoid aggregates of B cells become evident in the small airway wall. COPD is a neutrophilic disease in the airway and lumen, with also a large increase in luminal macrophages. Neutrophils are also found in mucus glands in abundance but in airway epithelium and smooth muscle bundles.[9] To our surprise, we found a decrease in the total number of cells in the lamina propria in current smokers, with and without COPD, compared to normal controls.[10] There has been no previous differentiation between the hyper-cellularity around the reticular basement membrane (RBM)[11,12] and the hypo-cellular in the underlying layer.[10] We are currently doing a comprehensive cellular analysis of lamina propria in COPD with recent data indicating low numbers of neutrophils in smokers with COPD.[10] Blood vessel density is also decreased in the lamina propria,[13] but we do not know if these two phenomena are related, i.e. fewer vessels meaning less cellular trafficking to lamina propria tissue.

Although there have been a number of studies reporting inflammation in COPD, it is still hard to draw any firm conclusions based on the current literature. Markers used in these studies are often controversial.[14,15] The lamina propria in COPD is associated with decreased cellularity at least in mild-to-moderate disease, except in specific areas such as glands and airway lumen. We suggest that the role of inflammation in COPD needs more work, especially teasing out exactly which type of cells are going down, and if this is a feature of only mild-moderate disease or of severe disease as well.

ROLE OF EPITHELIAL MESENCHYMAL TRANSITION (EMT) IN COPD

One of the features of chronic inflammatory airway diseases, including COPD, is airway remodelling.[16] In COPD, remodelling may occur as a response to smoking-induced damage to the airways, but the details of structural changes and underlying mechanisms are poorly described and understood.[17] One potential mechanism contributing to small airway fibrosis and epithelial malignancy (predominantly in large airways) is the transition of airway epithelial cells to a mesenchymal phenotype with myofibroblast characteristics, which then migrate into the lamina propria; a process termed EMT.[18] Milara et al.[19] recently reported that EMT is an active process in small airways of COPD patients and potentially contributes to small airway fibrosis. Wang and colleagues[20] further elaborated this concept by demonstrating increased urokinase-type plasminogen activator receptor expression in the small airway epithelium of patients with COPD, participating in an active EMT process. In our group, description of central airway remodelling, we observed hyper vascularity in relation to the RBM, i.e. EMT-Type 3. It is of note that large airways are classically the site of most lung cancers, especially squamous cell type.[21] Approximately 70% of patients with lung cancer have pre-existing mild-to-moderate COPD,[22,23] with COPD increasing cancer risk 6-fold, even allowing for the underlying smoking habit. We believe this link is under-appreciated and warrants further investigation.

Several pathways are proposed as a link between COPD and lung cancer.[22,24] Yang et al.[25,26] outlined pathways such as inflammation, tissue damage due to oxidative stress, altered DNA repair mechanism, and angiogenesis, as well as EMT being implicated in both COPD and lung cancer. EMT demonstrates many of these pathogenic processes suggested leading to lung cancer. Further, EMT caused both inhibition of growth arrest and apoptosis to increasing transitional cell survival. Such increased cell survival ultimately leads to tissue damaging pro-inflammatory cell necrosis, which itself can lead to an increased chance of malignant change.[27-31] Another important cancer modulator is the cancer-associated fibroblast (CAF), which plays a vital role in the development of solid cancer. Myofibroblasts or stromal cells derived from EMT, bone marrow derived blood fibrocytes, vessel endothelium derived stromal cells (Endo-EMT), or resident fibroblasts have all been proposed to be the

source of aberrant CAFs. These activated cells in 'pro-tumour stroma' facilitate angiogenesis, tumour induction, growth, and progression.[29,32] As already inferred; angiogenesis can be an important aspect of both premalignant and malignant phases of cancer development and, as described above, in large airways in COPD, EMT is associated with local angiogenesis, RBM, and epithelial hyper vascularity (EMT-Type 3). Hiroshima et al.[33] demonstrated angiogenesis and penetration of capillary loops into bronchial epithelium of smokers, who proved to be at high risk of developing lung cancer.

Proangiogenic vascular endothelial growth factor has been shown to be hyper expressed in bronchial and alveolar epithelial cell, airway smooth muscle cells of COPD.[34] RBM associated vessels were shown to be hyper permeable (positive for albumin), while those in the lamina propria were not.[35] This protein-rich tissue micro with fibrinogen extravasation may be stimulatory to angiogenesis.[36] A subsequent study found enhanced staining for transforming growth factor-beta-1 in RBM vessels in smoker COPD subjects, implicating it in this angiogenesis.[35] It is thought that endocan upregulation in blood vessel endothelium provides an immune defense for developing epithelial tumours by inhibiting accumulation and local activity of natural killer cells, which would otherwise keep check on tumour cell proliferation.[32,37]

THE EXTRACELLULAR MATRIX (ECM) IN COPD

Ultimately, the airflow limitation in COPD is the result of airway wall tissue remodelling and scarring, i.e. reorganisation of the ECM. These changes in the ECM have profound effects, the most important being gradual obliteration of the small airway. The cell type that is involved in ECM production is the myofibroblast. Studies in COPD based on this protein marker for myofibroblasts (alpha-smooth muscle actin [αSMA]) using human bronchi and bronchiolar tissue have been variable. Lofdahl et al.,[38] in their histological staining of large and small airway tissue from operative resection, showed an increased expression in αSMA positive cells in the lamina propria of the large airway in COPD patients when compared to non-smoker controls, although similar differences in the expression level were not observed in the small airway. In contrast, findings from *in vitro* studies with fibroblasts isolated from the distil end of the airway from COPD patients showed increased contractile properties associated with increased myofibroblasts.[39] These findings suggest myofibroblasts may be important in both the small and the large airways but the situation needs to be classified.

Myofibroblasts are known to secrete a large array of ECM proteins including fibrous proteins (collagens and elastin) and glycoproteins (fibronectin, tenascin C [TN-C], and proteoglycans). Fibrillar collagens Type 1, 2, 3, 5, and 11 are the most abundant matrix proteins and constitute approximately 15-20% of the dry weight of the tissue.[40] In patients with COPD, variability in collagen subtype deposition in both the large and small airways has been related to disease stage. In large airway biopsies, Harju et al.[41] observed an increase in expression of both collagens 1 and 3 in Stage 1 and 2 COPD in the lamina propria region, while Stage 4 COPD patients showed a decrease in expression of collagen 1 and an increase only in expression of collagen 3 when compared to normal smokers and non-smoker controls. Small airway tissues showed an overall increase in both collagen sub-types in the early stages (1 and 2), which subsequently decline in Stage 4. In contrast again, Annoni et al.[42] showed a decrease in collagen Type 1 and no change in Types 3 and 4 in mild-to-moderate COPD patients over that of non-smokers in resected tissue, in both large and small airways.

Recent evidence has shown that ECM glycoproteins, such as TN-C and fibronectin, have an essential role in tissue remodelling in COPD. Karvonen et al.[43] showed an increased expression of TN-C in mild-to-moderate COPD patients and increased correlation with myofibroblasts in the lamina propria area of the large airway biopsies. Similar changes were reported by Annoni et al.[42] For fibronectin, however, neither groups found any change in expression in COPD patients. Similarly, *in vitro* studies for evaluation of secretory fibronectin from fibroblasts isolated from non-smokers and COPD patients also showed no differences.[44] The findings are surprising as both glycoproteins are known to be secreted by myofibroblast, and the apparent differential expression level could be due to spatial and temporal changes that occur in the ECM under disease conditions.

Proteoglycans consist of a protein core covalently attached to one or more glycosaminoglycan (GAG) chain(s) and have an essential role in maintaining tissue homeostasis. Proteoglycans are further subdivided into three subtypes: basement

membrane proteoglycans (e.g. perlecan), small leucine-rich proteoglycans (e.g. decorin, biglycan, lumican), and hyalectans (versican, aggrecan).[45] Annoni et al.[42] recently observed no changes in versican, decorin, biglycan, or lumican expression in resected large or small airways or in lung parenchyma among COPD patients in comparison to non-obstructive smoker and non-smoker controls. In contrast, van Straaten et al.[46] had earlier observed a decreased expression of decorin and biglycan in the peribronchiolar area of the emphysematous lung tissues of COPD patients, and associated it to decreased elastic recoil and increase in bronchiolar obstruction. Further, Hallgren et al.[47] described that distal airway fibroblasts from COPD patients showed enhanced production of versican, which correlated with decreased elastic recoil emphysema. Lower perlecan production was observed from centrally derived cells in COPD.

Although there are substantial reports on ECM changes in other lung diseases such as interstitial lung disease (including idiopathic pulmonary fibrosis) and asthma, investigations into changes in the ECM in COPD patients are limited. The lack of differential markers to distinguish myofibroblasts from other fibroblasts and mesenchymal stromal cells has been an impediment to this research. New markers such as CD44 and CD90 (Thy1) have emerged as plausible specific tools that could improve sensitivity.[43,48] There is also great interest over recent results in the roles played by other mesenchymal cells, such as pericytes and endothelial cells, and their potential transition to myofibroblasts, and also the role of macrophage subtypes in maintaining and/or disrupting the ECM homeostasis in airway and lung tissue of COPD patients.

CHRONIC AIRWAY INFECTIONS IN COPD

Airway infection is not a primary driver of COPD, as tobacco smoking is, but it seems undeniable that chronic airway infection with either bacteria or viruses, or both, is important in the progression of disease. Lungs are 'sterile' based on traditional microbiological techniques, while potentially pathogenic microorganisms are present in lower airway secretions in 29-45% of COPD patients (sputum and bronchoalveolar lavage). The most common 'colonisers' in the stable state of COPD are *Haemophilus influenzae, Streptococcus pneumoniae,* and *Moraxella catarrhalis.*[49-53] Chronic airway 'colonisation' by respiratory viruses in COPD is controversial.[54] However, low-grade respiratory syncytial virus (RSV) infection in 30% of sputum samples in stable patients has been detected. Moreover, latent adenoviral infection has been proposed, and detection rates (approximately 6%) were similar in both stable COPD and exacerbations. Adding to this, lung tissue from COPD patients was found to carry more group C adenoviral DNA compared to non-obstructed smokers.[55] Recent applications of highly sensitive molecular techniques (e.g. reverse transcription polymerase chain reactions) have perspective on whether normal respiratory tracts are really sterile, with traditionally 'non-culturable' bacterial communities found in the human lung. The microbiome may alter in COPD but data are highly inconsistent across the various studies published so far.[56-59] It seems likely that in COPD there is decreased bacterial diversity as disease severity increases.[58,60] The main change seems to be an increase in *Haemophilus*, which is much the same conclusion for traditional culture methods.

COPD patients are prone to exacerbations, which are characterised by worsening dyspnoea, cough, and sputum (increased purulence) production, requiring antibiotic treatment.[61] Traditional microbial culture techniques have demonstrated that approximately 50% of COPD exacerbations are associated with increased bacterial loads, mainly *S. pneumoniae, H. influenzae*, and *M. catarrhalis*.[62] *Pseudomonas aeruginosa* becomes prevalent only in advanced disease.[63] In addition, exacerbations may very well be elicited by acquisition of a new bacterial species or by the acquisition of a different bacterial strain of an established bacterial species.[64] The pathogen-directed host innate-immunity is really the effector of acute exacerbations of COPD, leading to further lung injury and progression of airflow obstruction.[65] Novel diagnostic techniques based on the viral genome have highlighted that viruses likely initiate 22-64% of COPD exacerbations.[66] Of particular interest is rhinovirus, which makes up to 50% of the total viral genome isolated, followed by influenza, para-influenza, RSV, and adenovirus.[67] In addition, up to 25% of exacerbations occur when patients encounter a co-infection involving both bacteria and viruses, and are thus associated with more severe disease.[68] It would seem that the initial respiratory viral infection alters the host immunity by significantly increasing the levels of inflammatory cytokines and also enhancing bacterial adherence/proliferation.[50,62] Thus, bacterial-viral interactions

are associated with increased airway inflammation, bacterial load and symptoms, and comparatively more reduced lung function.[69]

Apart from bacterial and viral infections in COPD, there has also been a focus on the possible presence of atypical bacteria including *Mycoplasma pneumoniae*, *Chlamydia pneumonia*, and *Legionella pneumophila*.[70-73] Although convincing evidence is sparse, chronic colonisation with *C. pneumoniae* may be associated with more frequent exacerbations as well as amplified inflammatory responses in the airways of COPD patients, especially ciliostasis that promotes infection with other respiratory infections.[71]

ADHESION MECHANISM: A NOVEL RESEARCH AREA

An important question to address is why only a limited number of pathogens (mostly only three bacteria) actually gain access to the airways. Epithelial adhesion is a prerequisite for colonisation of mucous membranes, and one possible mechanism employed by 'the' major respiratory pathogens, *H. influenzae* and *S. pneumonia*, is adaptively enhanced airway epithelial adherence by physico-chemical interaction of phosphorylcholine on the bacterial cell wall surface with platelet activating factor receptors (PAFr) on the airway epithelial cells.[74]

Another major 'receptor' for pathogens is intercellular adhesion molecule-1, which is one of the important receptors for attachment and invasion of lung epithelia in >90% of Rhinovirus serotypes.[75,76] Some reports also suggest relevance for another receptor family, namely Toll-like receptors (TLRs), largely found on innate immune cells and structural cells. In this case, reduced TLR expression in COPD on airway inflammatory cells can lead to constrained and inadequate pathogen identification and clearance, facilitating bacterial colonisation, viral invasion, and an increased risk of exacerbations.[77] Several less investigated pathogen-sensing receptors include RIG-I-(retinoic acid-inducible gene 1)-like receptors (RLRs) and NOD (nucleotide-binding oligomerisation domain)-like receptors (NLRs).[78] RLRs are believed to be anti-viral, whereas NLRs are known to interact with bacteria. It may be that upregulation of such cell surface adhesion molecules and/or downregulation of innate immune pathogen-sensor receptors is key to pathogenesis of chronic colonisation and/or acute and chronic infection by 'pathogens' in COPD. This is a relatively new area of research in airway microbiology of COPD, but we have shown that PAFr is upregulated by cigarette smoke acting on epithelial cells, and expression of PAFr is especially marked in COPD.[74,79]

CONCLUSIONS

COPD is a disease of enormous international importance. Unfortunately, the international research effort into COPD has been disproportionately weak compared to its social importance, and is the least researched of all common chronic conditions. Tobacco smoking is the major aetiological factor for COPD in developed countries, but the clinical outcomes are poorly understood. To some extent, inflammation has been broadly studied in COPD but there are studies reporting contradictory results, which warrant further studies. The prime pathology associated with COPD involves destructive airway remodelling including obliteration of small airways. These individuals are also especially at risk of lung cancer, with approximately 70% of lung cancer occurring in this group. We believe that recent work on EMT in COPD may lead to a radical rethink of the airway pathology of COPD and its linkage to physiological dysfunction, destructive airway remodelling including obliteration of small airways, and also to lung cancer development; teasing out these mechanisms may have therapeutic implications. This will also lead to better understanding of the ECM changes in the airway wall. Current evidence suggests the role of chronic infection in the pathogenesis of COPD (both stable and exacerbations) in a considerable subset of patients but the underlying mechanisms, which increase the susceptibility to infections, are far from clear. As this research field advances in the future, we anticipate a better understanding of respiratory host-pathogen relationship; understanding of its detailed pathogenesis is needed to design better translational treatments and management strategies.

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INHALED AMBIENT PARTICULATE MATTER AND LUNG HEALTH BURDEN

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ABSTRACT

Increased ambient particulate matter (PM) has been associated with various cardio-respiratory disorders and emergency room visits due to short-term and long-term exposures. However, most of the efforts correlating PM exposure with human health hazards have primarily focused on cardiovascular impairments, although the lung acts as the primary port of entry, and is therefore also the primary target organ. Emerging evidences have shown an association between increased PM and respiratory illness, particularly chronic lung diseases. PM_{10}, $PM_{2.5}$, ultrafine particles, or nanoparticles (NPs) are of interest in this regard. Particle surface area increases with decreasing size and surface related parameters such as oxidative potency, solubility, and bioavailability, and are widely regarded as the parameters determining particle toxicity. Factory utility smoke stacks, vehicle exhaust, wood, and biomass burning act as the primary sources for ambient PM, coupled with composition variability. Revolution of nanotechnology during the last decade brought forward concerns about NPs as a potential new health hazard as well. Epidemiological, clinical, and experimental studies suggest oxidative stress, inflammation, impaired inflammation resolution, and altered coagulation cascade homeostasis as the causative mechanisms of both pulmonary and cardiovascular impairments due to PM exposure. Children, the elderly, and individuals with pre-existing conditions are found to be the most vulnerable subjects. Respiratory symptoms of increased PM exposure include increased infection, pneumonia, chronic bronchitis, emphysema, exacerbation of asthma and chronic obstructive pulmonary disease, declined forced expiratory volume in 1 second, and forced vital capacity, apart from the classically known phenomenon of asbestosis, silicosis, mesothelioma, lung cancer, and pneumoconiosis.

Keywords: Particulate matter, particle pollution, chronic lung disease, lung function, pulmonary inflammation.

INTRODUCTION

Particulate matter (PM) is a generic term representing the major portion of air pollution, which is made up of coarse but also extremely small particles, so called nanoparticles (NPs) - liquid droplets containing acids, organic chemicals, metals, and soil or dust.[1] Particles are present everywhere, but high concentrations, chronic exposure, and/or specific types of particles have been found to present serious human health hazards. Accidental inhalation of particles in the workplace or environmental exposure where the lung serves as the primary port of entry as well as the primary target, thereby causing chronic lung diseases, is the focus of this review. However, PM-mediated cardiovascular (CV) effects are by far most widely investigated. Quartz or crystalline silica, asbestos, and coal are the three major particle types classically considered to be responsible for the vast majority of occupational and particle-induced lung diseases.[2-4] Silicosis is caused primarily through silica exposure, particularly among miners. Asbestos exposure is causative for asbestosis,

lung cancer, pleural fibrosis, pleural plaques, and mesothelioma.[5] Exposure to coal mine dust causes a form of pneumoconiosis along with emphysema. Towards the end of the 20th century, toxicological studies on environmental particles (PM_{10}) gained momentum after the rulings of various regulatory authorities affirming the lung disease relationship following silica, asbestos, and coal dust exposures.[6] Subsequently, researchers also demonstrated an association between small variations in air pollution concentration and health effects such as heart attacks and exacerbations of asthma.

Ambient PM is a complex mixture of dust, ashes, and volatile and gaseous compounds, which come from diverse sources (factory/utility smokestacks, vehicle exhaust, wood burning).[7] However, the composition of ambient PM also varies temporally depending on the seasonal condition, traffic density, and localised industrial and human activity. Air pollutants or ambient PM are respiratory irritants and increase susceptibility to acute respiratory infections and chronic lung diseases, particularly among compromised individuals.[8] The effects of ambient PM on human health is a major concern as particles <10 μm (PM^{10}) and <2.5 μm ($PM^{2.5}$) in aerodynamic diameter gain access to the deep lung. The US Environmental Protection Agency[1] listed the links between particle pollution exposure and a variety of health problems, including: premature death in people with heart or lung disease, nonfatal heart attacks, irregular heartbeat, aggravated asthma, decreased lung function, and increased respiratory symptoms, such as irritation of the airways, coughing, or difficulty breathing. People with pre-existing heart or lung diseases, children, and elderly individuals are the most vulnerable subjects for particle pollution exposure-related health risks. Healthy individuals may also experience temporary symptoms from exposure to elevated levels of particle pollution. Ultrafine particles (UFPs; <0.1 μm), also referred to as NPs following nano-technological revolution, contribute very little to the overall PM mass but more to PM number concentrations. UFPs have emerged as an important modern day air pollution hazard, mainly by virtue of their property to evade the effective mechanisms of mucocilliary and alveolar clearance of the lung, compared to larger particles. Through our current understanding, PM exposure contributes to respiratory morbidity and mortality primarily through oxidative stress and inflammation which, in turn, may even result in anatomical and physiological remodelling of the lung. The localised particle-triggered reactions in the lung have been shown to contribute to systemic effects particularly by disturbing the homeostasis of the blood coagulation cascade, thereby causing atherogenic reactions and cardiac impairments. The current knowledge on ambient PM-mediated lung health burden is primarily based on epidemiological, clinical, and experimental findings. In this review we addressed the topic broadly based on these three lines of evidence with emphasis on lung health burden.

EPIDEMIOLOGICAL EVIDENCE

The relationship between increased levels of air pollution and mortality/morbidity rates due to cardiopulmonary diseases is now well-established. To date, most of the effort in PM toxicology/PM-mediated health risk has focused on the CV system,[9,10] although many studies evaluated the association between PM exposure and respiratory illness.[11,12] Most of these studies reported that the emergency hospital admission in association with increasing ambient PM is mainly because of pneumonia, asthma, chronic inflammation, and chronic obstructive pulmonary disease (COPD). Exposure to PM shows a strong association with adverse respiratory health effects even when adjusted for other major risk factors such as cigarette smoking. Acute exacerbations of COPD (AECOPD), chronic bronchitis (CB), or emphysema have been associated with short-term exposure to air pollution. It has been reported that high levels of ambient particles are related to increased prevalence of CB, whereas recent studies predominantly related respiratory symptoms to the long-term effects of ambient particles. Several cross-sectional studies associated exposure to ambient urban traffic-related PM with declined forced expiratory volume in 1 second (FEV1) and onset of COPD. Schikowski and colleagues,[13] using the Global Initiative for Chronic Obstructive Lung Disease criteria, showed, in a cross-sectional study among women, that an increase of 7 $\mu g/m^3$ ambient PM (over 5 years) was associated with a 5.1% decline in FEV1 with an odds ratio of 1.33 for the development of COPD. Furthermore, they also associated that inhabiting <100 m away from busy traffic areas had significant detrimental effects on lung function. These findings suggest that both long-term exposure to ambient PM and habitation close to busy traffic may increase the risk of COPD progression and also accelerate a loss of lung function. Increased concentration of PM has been shown to be directly correlated to an increased mortality among individuals with

pre-existing COPD. Lee et al.[14] have shown that asthmatics living in areas of high PM in London had significantly higher reductions in FEV1, forced vital capacity (FVC), and increased inflammatory response. A series of studies have reported that elderly patients or patients with pre-existing complications (viz. COPD) exhibit an accelerated decrease in lung function with an increase in $PM_{2.5}$ concentration.[15,16]

Gauderman et al.[17] performed an explorative study on PM mediated respiratory risk over 1,759 children and found a strong association between reduced annual growth of FEV1 in children over the age of 8 and exposure to elemental carbon, nitrogen dioxide, and acid vapours. Islam et al.[18] reported that sudden exposure to a highly polluted area (PM_{10} and $PM_{2.5}$) can result in new onset of asthma, even in children with better lung function. Goss et al.[19] demonstrated that predisposed children with lower lung function developed cystic fibrosis following exposure to higher levels of PM_{10} and $PM_{2.5}$. Through the course of the children's respiratory health study, Grigg et al.[20] reported that chronic exposure to indoor PM following biomass burning (200 mg/m^3) can lead to COPD, impaired lung function, and induce lung infection. There is mounting evidence suggesting that PM exposure leads to pulmonary inflammation and oxidative stress. Lung inflammation and redox imbalance plays a pivotal role in the development of chronic lung diseases such as asthma and COPD. Measurement of oxygen saturation in arterial blood was shown to be an important parameter to assess the respiratory risk or air pollution induced pulmonary burden. Decrease in oxygen saturation in arterial blood in association with PM_{10} exposure at Utah valley was first reported by Pope et al.[21] Similar findings have been also reported by DeMeo et al.[22] through a study on 28 elderly Boston residents.

A series of studies on European, Asian, and Oceania cities have demonstrated a consistent and significant association between PM concentrations and emergency room visits for respiratory diseases such as chronic pulmonary inflammation.[23-25] Accumulated evidence suggests that these PM induced chronic pulmonary inflammations may lead to further lung diseases - such as asthma, pneumonia, and COPD - and the effects are more pronounced among elderly patients, even following short exposures.[26] Recently, Hoek et al.[27] estimated the $PM_{2.5}$ mediated respiratory mortality in a Dutch, Norwegian, and Chinese cohort study. The Norwegian study by Naess et al.[28] has demonstrated an approximate 17% increase of respiratory mortality due to acute COPD for every quartile increase in $PM_{2.5}$. Similar results for increased respiratory mortality have been found in Asian cities where researchers have demonstrated excess respiratory mortality risk for increases in PM_{10}.[29] A cross-sectional study in India reported a significant negative linear relationship between higher concentrations of PM_{10} with reduced FEV1 and increased concentration of $PM_{2.5}$ with reduced peak expiratory flow rate and FEV1.[30] A 2.5% increase in COPD admissions for every 10 $\mu g/m^3$ increase of PM_{10} was observed with a lag of up to 0-5 days in an American study involving 10 cities and >1.84 million individuals >65 years of age.[31] In another study, every 10 $\mu g/m^3$ increase of $PM_{2.5}$ was associated with 0.9% increased COPD hospitalisation with a lag of 0-1 day.[32] In a European study involving six cities, the relative risk (95% CI) for 50 $\mu g/m^3$ increase in the daily mean level of total suspended PM for AECOPD admissions was 1.02 with a lag of 1-3 days.[33] All these epidemiological studies demonstrated that the observed respiratory mortality is primarily due to the fraction of traffic-related pollutants.

Only very few studies have linked genes and respective polymorphisms to PM toxicity. Curjuric et al.[34] associated single nucleotide polymorphisms located in *SNCA*, *CRISP2*, and *PARK2* to declined FEV1/FVC and FEV1 following PM_{10} exposures in the Swiss Study on Air Pollution and Lung and Heart Diseases in Adults. However, more epidemiological studies are warranted, especially those including particle quality, which are related to workplace and NP exposure to evaluate the long-term effect of PM and lung burden.

EXPERIMENTAL EVIDENCE

Epidemiological studies have established the close association between ambient PM exposures to respiratory diseases such as asthma, COPD, lung cancer, and declined lung function, apart from CV diseases. To substantiate the epidemiological associations and detect the plausible pathomechanisms causative of respiratory illness, researchers performed controlled human studies, animal exposures, and *in vitro* experiments. Particle exposure experiments mainly addressed two aspects: 1) oxidative stress and proinflammatory response; and 2) particle characteristics related to toxicity. Another phenomenon termed as translocation - where particles enter the deep lung, cross the alveolar-blood barrier to enter

systemic circulation, and thereby reach secondary target organs (heart, liver, kidney, and brain) - is an important aspect of particle toxicology and particularly relevant for sub 100 nm sized NPs. Even if particle translocation has been described only for NPs, its efficacy is considered to be low and far less than 1% of the pulmonary deposited dose, which may actually translocate to extra-pulmonary organs. In this context, long-term exposure and accumulation have to be considered.[35]

Oxidative Stress Paradigm

Oxidative stress, leading to activation of pro-inflammatory reaction, is the most reported pulmonary effect of inhaled ambient PM. In this context, Li et al.[36] described the use of a stratified oxidative stress model to study the biological effects of ambient PM. This hierarchical and tier-based model suggests that the level of particle cell-interaction derived oxidative stress and the ability of the cell and tissue to cope with that stress, finally determines whether, upon PM inhalation, only anti-oxidant (tier 1), or pro-inflammatory (tier 2), or even cytotoxic responses (tier 3) are caused. Tao et al.[37] reported that activation of alveolar macrophages by particles leads to a release of proinflammatory/inflammatory cytokines and a production of reactive oxygen species. Particle charge, presence of transition metals, organic components, size, and surface area are considered to be defining properties for particle toxicity.[38] In ambient air, fine and UFPs are predominantly based on the number concentration among all particles, and represent the highest surface area per mass. Studies from Brown et al.,[39] Tran et al.,[40] and Renwick et al.[41] established the idea of particle surface area instead of mass as the optimal dose metric for predicting the acute inflammatory response in the lungs (reviewed by Oberdörster et al.[38]).

Later, Stoeger et al.[42] investigated the acute adverse effects of six similar types of carbonaceous UFPs quantitatively following intratracheal (i.t.) instillation in healthy mice. The authors also concluded that the surface area measurement developed by Brunauer, Emmett, and Teller (BET) is a valuable reference unit for assessing the toxic effects of carbonaceous UFPs. BET surface area exhibited the most obvious dose-response relationship to the inflammatory effect in this study. From this result, the authors suggested particle surface area to be the most important parameter for evaluating the detrimental health effects caused by inhaled UFPs. Stoeger et al.[43] further established an *in vitro*, cell-free ascorbate test for measuring oxidative potency (Ox_{pot}) of particles using different types of combustion-derived NPs. For ambient particulate air pollution, however, it needs to be taken into account that the different size fractions also differ significantly in their composition and that these particles are not necessarily as non-soluble as carbonaceous model particles. Urban UFP samples, which mainly originate from combustion processes, consist of not only carbon but also metal oxides such as zinc and iron, as well as biological components, such as endotoxin. Investigation on the inflammatory potency of ambient PM samples therefore often reflects the amount of contained endotoxin,[44] and the presence of particular metal oxides (such as ZnO) may also contribute to their cytotoxicity.[45]

Impact of Particle Size

Particle size is another important parameter driving the spatial deposition pattern within the respiratory system.[46] Fine and ultrafine inhaled PM deposits most effectively in the alveolar region of the lungs (~50% deposition efficiency for 3 μm and 20 nm particles). Alveolar macrophage mediated clearance is described to work most effectively for microparticles compared to NPs. This explains why chronic exposures to high concentrations of NPs have been shown to cause the so called 'overload conditions', with impaired particle clearance and accumulation finally leading to chronic inflammation and even tumour development in rats.[47] These conditions occur as the cumulative deposited particle volume exceeds a threshold of 6% of the alveolar macrophage volume of the lungs.[48] At 40% of the macrophage volume, the mucociliary clearance (which is intrinsically slow in nature) for materials deposited in the alveolar zone comes to a complete standstill, causing extreme burden for the sensitive area(s) of the respiratory tissue. It must be noted that because of the biphasic clearance mechanism, clearance of the airway is fast and is characterised by a half-life for bronchiolar deposited particles <1 day, whereas the alveolar half-life is 700-900 days, or even longer for diseased individuals.[49,50] Due to their small size, UFPs are known to enter deeply into the lung and eventually can cross the alveolar–capillary barrier, thereby directly interacting with extra-pulmonary organs and resulting in CV/cerebrovascular impairments in susceptible individuals. Kreyling et al.[51] showed that translocation of UFPs across the air-blood barrier, and their accumulation/retention in the

secondary organ, is highly dependent on the particle characteristics such as size and surface charges.

EPIDEMIOLOGICAL AND ANIMAL STUDIES

A series of epidemiological and experimental studies have proposed that exposure to ambient PM results in pulmonary inflammation, lung injury, and procoagulant changes in the lung, which may finally lead to the observed cerebrovascular/CV effect. Therefore, it is conceived that PM mediated pulmonary inflammation or alteration of pulmonary homeostasis plays a central role in PM mediated localised lung burden as well as systemic burden. Gilmour et al.[52] have suggested that increased levels of systemic fibrinogen or impaired blood coagulation in Wistar Kyoto rats may be due to pulmonary inflammation and injury following exposure to ZnO particles. Similarly, Budinger et al.[53] reported that inhalation of ambient PM results in interleukin-6 (IL-6) and tumour necrosis factor-alpha dependent lung and systemic activation of coagulation and prothrombotic state. Exposure of concentrated ambient particles (CAPs) on normal (F344) rats and hypersecretory airway (BN) rats showed no significant CAP mediated toxicity or inflammation in ovalbumin treated F344 rats.[54] However, significant increases in airway mucosubstances and pulmonary inflammation were observed in ovalbumin-challenged BN rats. This study demonstrated that adverse biological response to $PM_{2.5}$ is highly dependent on the local sources of particles as well as the conditions supporting the epidemiological findings.

Several epidemiological studies indicated individuals with impaired lung function to be more susceptible to respiratory illness such as COPD following PM exposure.[55-57] To approach this observation in an experimental setting, Ganguly et al.[58,59] exposed two inbred mouse strains (C3H/HeJ and JF1/Msf) with extremely divergent lung function, as identified in the Mouse Phenome project, to CNP of moderate toxicity by i.t. instillation. Assessment of a comprehensive panel of proinflammatory cytokines and bronchoalveolar lavage cell differentials over a time course revealed impaired polymorphonuclear leukocyte resolution kinetics in JF1/Msf mice with lower lung function. Furthermore, at a time point when C3H/HeJ mice, with higher lung function, were able to resolve the inflammatory challenge completely, a sudden and sharp influx of macrophages and lymphocytes, symptomatic of chronic lung diseases, was detected in the airspace of JF1/Msf mice. This differential response between the divergent lung physiological states was attributed to a defence/homeostatic response involving IL-1β and IL-18, vascular endothelial growth factor, fibroblast growth factor 2, and endothelin in C3H/HeJ mice, which was absent in JF1/Msf mice. The contrasting effects of CAP (from two separate locations) on allergic airway response was observed by Wagner et al.[60] Exposure to CAP from both collection sites did not show any adverse pulmonary effect on non-allergic rats, whereas asthmatic rats showed a 200% increase of lung mucus along with influx of neutrophil, leucocytes, and protein leakage. This study therefore revealed that the pulmonary reaction and burden not only depended on the specific chemical components and size distributions of urban $PM_{2.5}$ but also on the sensitivity of exposed individuals.

Xu et al.[61] have shown exposure to diesel exhaust particles (DEPs) induces an adverse respiratory effect, such as irritation, reduced peak expiratory flow, and upregulation of inflammatory markers, within 75 minutes of controlled exposure. According to the estimates from US, DEP emissions constitute 4-16% of the total PM in non-urban and urban areas. The Umeå study by Sehlstedt et al.[62] has provided extensive knowledge on the respiratory effects of an even moderate DEP exposure. The absence of lung function changes in conventional tests in most of the Umeå studies may have been due to the relatively short exposure and follow-up times. Overall, it is imperative that both outdoor (e.g. motor vehicle emissions) and indoor (e.g. cooking gas) air pollution play pivotal roles in onset, exacerbation, and progression of cardiopulmonary complications, with elderly or susceptible individuals being at the highest risk.

CONCLUSION

In summary, ambient PM exposure has been correlated to various respiratory diseases and symptoms such as asthma, COPD, and declined lung function. An efficient environmental risk evaluation will also need to consider the sensitivity and susceptibility of the exposed individuals, in addition to the conventionally used criteria such as: 1) the hazard or toxicity of air pollutants; and 2) specific exposure characteristics. Accordingly, numerous epidemiological studies describe the most significant pollution-related health effects for elderly and cardiopulmonary susceptible individuals.

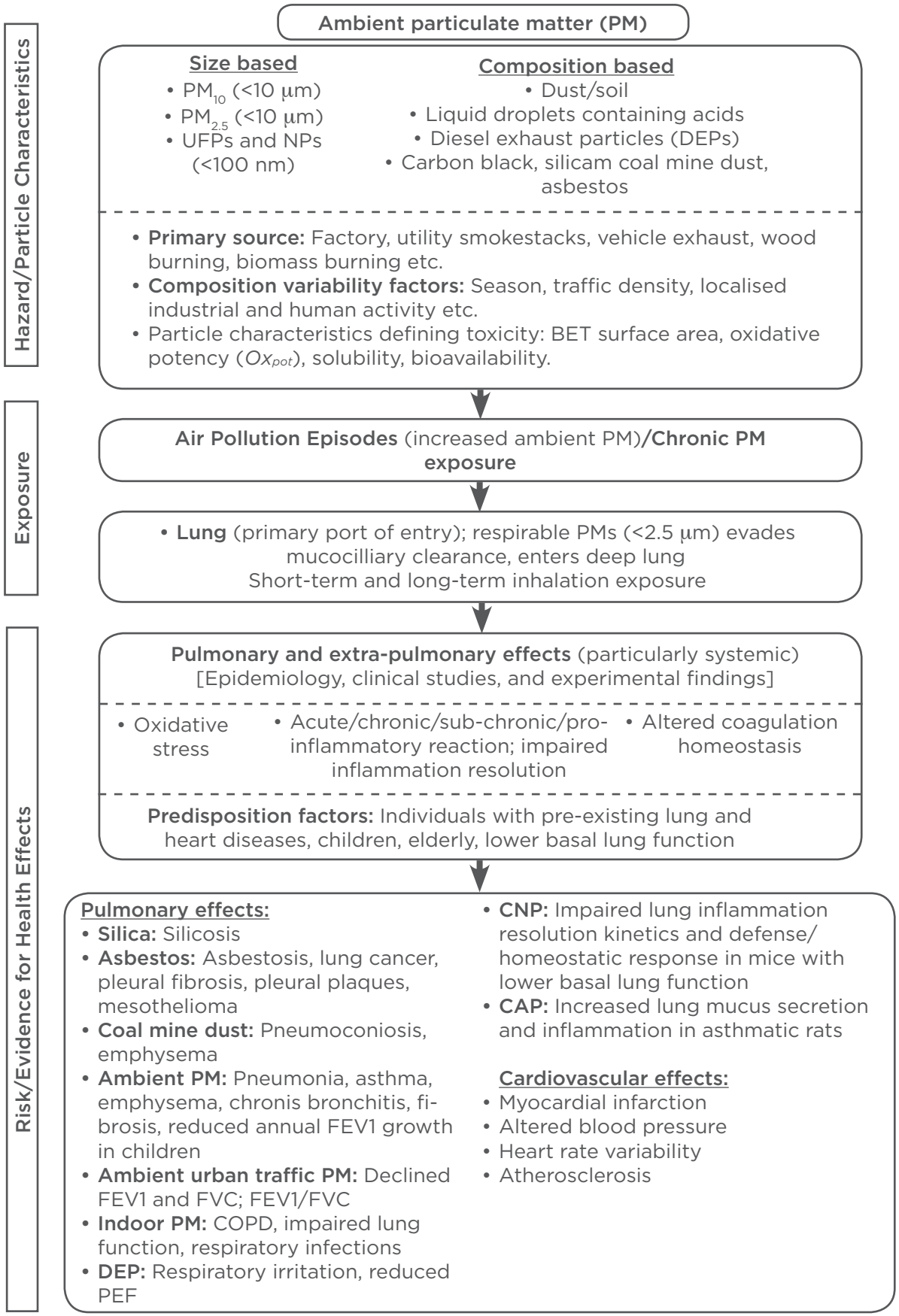

Figure 1: Summary sketch of the ambient particulate matter related lung health risk.

UFP: ultrafine particle; NP: nanoparticle; BET: Brunauer-Emmett-Teller measurement; CNP: carbon nanoparticle; CAP: concentrated ambient particle; FEV1: forced expiratory volume in one second; FVC: forced vital capacity; COPD: chronic obstructive pulmonary disease; PEF: peak expiratory flow.

Oxidative stress and pulmonary inflammation are by far regarded as the major mechanistic events driving the pathomechanism, as supported by epidemiological as well as experimental findings (Figure 1). BET surface area and Ox_{pot} measured in cell free systems may serve as important PM toxicity indicators. The physiological status of the lung, as indicated by basal lung function or pre-existing condition, is also an important parameter to assess susceptibility to ambient PM that may be related to an inefficient inflammation resolution capacity or extent of an allergic response.

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INFLUENCE OF AIR POLLUTION ON RESPIRATORY DISEASE

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ABSTRACT

A large number of individuals live in areas of poor air quality, especially in urban environments. Such residency is linked with the exacerbation of asthma, respiratory morbidity and mortality in patients with chronic obstructive pulmonary disease (COPD), and increased risk of viral respiratory infections. Recent studies, again particularly in urban areas, suggest a role for air pollution in the development of both asthma and COPD. In cities the major pollutant of concern is particulate matter (PM), which in both Europe and North America arises mostly from traffic, while in Asia biomass combustion also makes an important contribution. No matter the source, PM exposure can give rise to oxidative stress in the airways. Recent advances in understanding the mechanisms implicated in the association of air pollutants and airway disease include epigenetic alteration of genes by combustion-related pollutants and how polymorphisms in genes, involved in antioxidant pathways and airway inflammation, can modify responses to air pollution exposures. Other interesting epidemiological observations related to the increase of host susceptibility include a possible link between chronic PM exposure during childhood and vulnerability to COPD in adulthood, and that infants subjected to higher prenatal levels of air pollution may be at greater risk of developing respiratory conditions. As medical research continues to expand links between air pollution and an increased incidence and/or severity of airway disease, there is an ongoing need for policy initiatives to improve air quality. Furthermore, accessible, easy to interpret, and engaging information systems are needed to help individuals with respiratory conditions to make informed choices about their behaviour, in a way that improves their health as well as the quality of the air they breathe.

Keywords: Particulate matter, nitrogen dioxide, ozone, asthma, chronic obstructive pulmonary disease (COPD), respiratory infection, oxidative stress.

INTRODUCTION

In the past few decades, global urbanisation requiring intense energy consumption has resulted in increased emissions into the atmosphere and a decrease in urban air quality. As a consequence, hundreds of millions of individuals experience an increased quantity, but also a more diverse variety of ambient air pollution. The air pollutants of most concern include ozone (O_3), nitrogen dioxide (NO_2), and particulate matter (PM). Ozone is a major constituent of photochemical smog and is generated at ground level by atmospheric reactions of NO_2, hydrocarbons, and ultraviolet light. The major source of NO_2 and PM is fossil fuel combustion, primarily from motor vehicles, in addition to energy generation and industry; while in many parts of the developing world, exposure to household biomass combustion for cooking and heating is the major source.[1] The Global Burden of Disease Study[2] reported that PM exposure was the fourth biggest threat to the health of the Chinese population with 1.2 million people dying prematurely in 2010.

Of these common urban air pollutants, PM has been studied in the greatest detail, but there is increasing awareness of independent and direct health effects of NO_2. PM is a general term that refers to a complex mixture of solids or liquids that vary in number, size, shape, surface area, chemical composition, solubility, and origin.[3] The main components of PM, originating from road transport, are engine emissions, brake and tyre wear, and dust from road surfaces. The largest single source of airborne PM from motor vehicles is derived from diesel exhausts, and this is an increasingly important problem in Europe.[4] Owing to the growth in the number of new cars with diesel engines, diesel exhaust particles (DEPs) account for the most airborne PM in most European cities. Biomass combustion particles have a range of physiochemical properties, depending on the nature of the biomass and combustion conditions which, in turn, influences PM toxicity.

The inhalation of toxic particles and gases targets the natural defences of the lung by increasing epithelial permeability, decreasing mucociliary clearance, and depressing macrophage function. Although individual air pollutants will exert specific toxic effects on the healthy or diseased respiratory system, a common chain of molecular events ensue. Human, animal, and *in vitro* experimental studies have demonstrated an increased recruitment and activation of inflammatory cells, and the generation of an array of inflammatory mediators, as well as the activation of intracellular oxidative stress via the generation of free radicals and depletion of protective small molecular weight antioxidants,[5] and antioxidant enzymes.[6] Oxidative stress, in turn, promotes further inflammation via regulation of redox-sensitive transcription factors and signalling via the mitogen-activated protein kinase pathway. DEPs and O_3 are able to increase the production of the allergic antibody immunoglobulin E (IgE), thereby increasing sensitisation to allergens.[7,8] With widespread urban air quality problems across Europe, it is perhaps not that surprising, therefore, that we are experiencing an increased incidence of airway disease, which in turn provides continued momentum to the extensive research effort in this area.

RESPIRATORY SYMPTOMS AND LUNG FUNCTION

In children, epidemiological studies have demonstrated a strong association between exposure to particulate air pollution and cough and wheeze;[9,10] improvement in air quality in Switzerland was found to result in fewer cases of chronic cough in children,[11] as well as cough, wheezing, and breathlessness in adults.[12] Exposure to O_3 at concentrations found in ambient air is associated with a reduction in lung function and induction of respiratory symptoms including cough, shortness of breath, and pain in deep inspiration.[13-17] Human toxicological studies suggest that effects diminish with increasing age, emphasising the importance of ventilation rate, and confirming the intrinsic differences in responsiveness to O_3 among individuals.[13,18,19] NO_2 concentrations have also been associated with cough, wheeze, and shortness of breath in children. Residential traffic-related air pollution exposure, associated with reduced expiratory flows in school children[20] and children relocating to areas of differing air pollution levels, have been reported to experience changes in lung function that mirrored changes in PM exposure.[21] The Southern Californian Children's Health Study (CHS)[22] was first to indicate that urban air pollution has lasting adverse effects on lung development in children, an important finding that is now supported by work from UK (Manchester)[23] and Japan.[24]

Asthma

The role of air pollution in the development of asthma has long been unclear. Recent studies, with a focus on urban areas, however, have begun to report consistent associations. Three European birth cohort studies have reported a positive relationship between traffic-related pollution and doctor-diagnosed asthma.[25-27] The CHS has reported that traffic-related pollutants can cause asthma in children,[22,28] as has a Dutch study in which traffic-related pollution levels at the birth address and incidence of asthma were considered during the first 8 years of life.[29] Not all studies, however, show such a relationship,[30] and such inconsistencies may be due to incomplete exposure assessment or insufficient study power as only a small number of children are likely to be particularly susceptible to the effects of air pollution. Host characteristics that have been implicated to influence the effects of air pollution on asthma include nutritional status, atopy, and social stress.[31-37]

The observation that social stress and traffic-related air pollution are often spatially correlated has prompted research into possible synergies between these two environments. Chronic stress has been

found to modify the risk of asthma associated with traffic-related air pollution exposure;[34] however, findings are not consistent.[35-37] Personal exposures of pregnant women to polycyclic aromatic hydrocarbons (PAHs) have been associated with increased respiratory symptoms,[38] such as asthma, wheeze, cough, and ear infections,[39] among their children over the first year of life. The first trimester (i.e. PM up to 10 micrometres in size [PM_{10}]) and second trimester (NO_2 exposures) were associated with lower lung function parameters in asthmatic children at an age of 6-11 years.[40] These epidemiologic observations are supported by mechanistic findings in mice. Prenatal exposures to PM or DEPs result in higher IgE levels, skewed T helper 2 cytokine responses, impaired lung growth, greater airway hyperresponsiveness, and increased infiltration of inflammatory cells.[41-43] Exposure of pregnant dams to PM has also been found to increase O_3-induced airway hyperresponsiveness, pulmonary cytokines, and epithelial mucous metaplasia in O_3-exposed pups,[44] whilst prenatal exposure to *Aspergillus fumigatus* allergen and/or DEPs appears to result in protection from developing systemic and airway allergic immune responses in the adult offspring.[45] These various observations fit with the report of immature antioxidant defences in the foetus.[46]

Clear strong linkages have been established between air pollution and exacerbation of asthma. Moreover, epidemiological studies point to several potential causal agents for the observed association. Ozone exposure has been linked with hospital admissions,[47,48] worsening of symptoms and rescue medication,[49] as well as asthma attacks, respiratory infections, and reductions in peak flow rate.[50] NO_2 exposure has been associated with emergency room visits, wheezing, and medication use amongst children with asthma,[51,52] whilst controlled-exposure studies of asthmatic volunteers have found that NO_2 can enhance the allergic response to inhaled allergens.[53,54] Evidence of adverse effects of particulate pollution include a negative effect on respiratory function[55] and associations with increased symptoms or hospitalisation.[56] A current key area of research is a focus on the specific relationship between asthma and traffic-related pollutants in urban areas.[57] A recent advance in assessing the effects of air pollution on asthma is the use of biomarkers of airway inflammation and oxidative stress as outcome measures in epidemiological studies.[58,59] Parameters such as distance to a major road or land-use regression models to predict concentrations of traffic-related pollutants among unmonitored individuals are also important developments in air pollution epidemiology.

The important contribution of traffic emissions to urban air pollution has led investigators to examine the relative toxicity of traffic-related PM pollutants. High previous-day concentrations of ambient air zinc have been associated with risks of paediatric asthma exacerbations,[60] while a positive association between ambient concentrations of vanadium, elemental carbon or nickel $PM_{2.5}$ content, and respiratory symptoms or hospitalisations has been reported.[61,62] The effect of size distribution and total number concentration of ultrafine and accumulation mode particles on respiratory hospital admissions in asthmatic children has also been considered.[63] For paediatric asthma, accumulation mode particles and NO_x are relevant, whereas PM_{10} appeared to have little effect.

Polymorphisms in genes involved in antioxidant pathways, airway inflammation, and innate immunity may modify an individual's response to air pollution. Polymorphisms in glutathione S-transferases (*GSTM1* and *GSTP1*) that facilitate the elimination of reactive oxygen species have been associated with breathing difficulties and respiratory symptoms in asthmatic children following increases in ambient O_3 concentrations[64] and an altered response to combined exposures to ragweed pollen and DEPs.[65] *GSTP1* polymorphisms have also been associated with a greater risk of asthma[66] and sensitisation to allergen in association with traffic-related NO_x during the first year of life.[67] In a study in Mexico City, *GSTM1* polymorphisms have been shown to predict asthmatic patients who will benefit from antioxidant supplementation.[65] Polymorphisms in the inflammatory gene for tumour necrosis factor-α and transforming growth factor β may influence lung function to ozone exposure[68] and risk of asthma in children living within 500 m of a major road,[69] respectively. With respect to innate immunity, the absence of measurable CD4 expression on circulating neutrophils in asthmatic children correlated with reduced lung function in the presence of ambient PM.[70]

Chronic Obstructive Pulmonary Disease (COPD)

Large-scale prospective studies used to examine the relationship between air pollution and the development of COPD have provided conflicting outcomes. Whilst the European Community and Respiratory Health Survey[71] did not find a

significant association between urban background air pollution and changes in forced expiratory volume in 1 second (FEV_1) and forced vital capacity, the Swiss Cohort Study on Air Pollution and Lung Diseases in Adults[72] did - reporting a significant negative association between decreased PM_{10} and the rate of age-related decline in FEV_1. A 7 μg/m³ increase in exposure to ambient PM_{10} over 5 years resulted in a more rapid decline in pulmonary function, a high-risk ratio to develop COPD, and poorer respiratory health in women living near high traffic areas or industrial sources.[73] One possible reason for these differing findings is the possible influence of early life exposures on COPD development.[74] It is clear that PM exposure both impairs normal lung function growth in children[22] and accelerates the natural decline in adult lung function.[75] It has been hypothesised that, in turn, a reduced lung function growth impairs the innate immunity of the lung and increases vulnerability to infection, possibly as a consequence of increased nasopharyngeal carriage.[76,77] In support of the latter, there is evidence from both the developing and developed world that exposure to PM increases susceptibility to bacterial infection in children.[78,79] Epidemiological evidence is also accumulating that infants subjected to higher prenatal levels of air pollution may be at greater risk of developing respiratory conditions. A birth cohort study found that prenatal ambient PAHs and $PM_{2.5}$ exposures led to neonates having a reduction in T cells and a concomitant increase in B lymphocytes and changes in cord serum IgE levels.[80]

COPD patients exposed to increased PM concentrations experience a worsening of symptoms and higher morbidity as assessed by emergency room visits or hospital admissions.[81-84] Worsening of the condition has also been demonstrated in several panel studies, reporting decreases in pulmonary function,[81] heightened night-time chest symptoms,[85] and increased rescue bronchodilator use.[86] Dominici and workers[83] reported almost a doubling of admissions for COPD exacerbations for every 10 μgm³ of increase in $PM_{2.5}$. Overall, epidemiological evidence also indicates an elevated mortality rate among individuals with COPD following exposure to PM,[87-89] although data collected from the American Cancer Society as part of the Cancer Prevention Study[90] were unable to detect such an association. It has also been observed that an effect of PM on mortality amongst COPD patients may be more pronounced among individuals with a lower income and socioeconomic status.[91] In addition to the well cited detrimental effects of PM, both O_3 and NO_2 have also been associated with increased hospital admissions[75] and respiratory mortality in patients with COPD.[92] Polymorphisms in the antioxidant gene coding for glutamate-cysteine ligase as well as *GSTM1* and *GSTP1* correlate with the risk of COPD.[93-95]

Respiratory Infection

Numerous epidemiological and experimental studies indicate an association between exposure to the common air pollutants and combustion products of biomass fuels, and an increased risk for viral respiratory infections.[96] Positive observations have been found between pollutant exposures and rates of chronic cough and bronchitis[97] in addition to admissions for pneumonia and influenza.[98,99] Acute increases in PM concentrations have been shown to significantly increase hospital admissions for respiratory infections.[83,100] There is also epidemiological evidence linking indoor exposure to air pollutants from the combustion of biomass fuels to pneumococcal infection.[101] A meta-analysis of studies in the developing world estimated that the odds ratio for severe pneumonia in children exposed to biomass smoke and other high PM-emitting fuels is 1.78 (95% CI, 1.45–2.18).[79] Furthermore, associations between exposure to biomass combustion and death due to respiratory infections in children have been reported,[102-104] as well as observations suggesting that NO_2 could enhance the severity of viral-induced asthma.[105]

Experimental studies in humans, animals, and *in vitro* reinforces the epidemiological evidence that air pollution can significantly affect susceptibility to and morbidity from respiratory infection. NO_2 has been shown to increase the morbidity of Sendai virus in mice,[106] whilst synergism between NO_2 (and O_3) and rhinovirus infection in human basal and bronchial epithelial cells have been found.[107] Carbon black and concentrated ambient particles have been shown to augment respiratory syncytial virus infection in mice,[108] reduce the capacity of macrophages to phagocytise this virus,[109] and reduce *Streptococcus pneumoniae* clearance from the lungs of mice.[110] Numerous studies of DEPs have reported increased susceptibility and response to influenza infection in mice and in human respiratory epithelium.[111-113]

Several potential mechanisms exist that may be involved in an environmental pollutant-induced

alteration of host immunity. Oxidative stress, particularly within the protective epithelial lining fluid of the lung,[113,114] is supported by observations of a protective effect of antioxidants to DEP-induced enhancement of influenza infections.[112] Alternatively, air pollutants may modulate the antiviral defences by reducing the ability of macrophages to phagocytise viruses.[109] Other important components of innate immunity which have been shown to be a target for air pollutants are the surfactant proteins SP-A and SP-D[115] and epithelial cell tight junctions.[116]

LOOKING FORWARD

Modern urban air pollution is a serious public health hazard. Furthermore, as adverse effects on the respiratory system have been observed at concentrations below ambient air quality standards, it appears that current legislation should be more stringent, and that pollution control strategies should focus on specific sources and constituents deemed to be most damaging. Specific areas of research that will prove invaluable if the effects of air pollution on airway disease are to be reduced, include identifying the most predictive exposure methods as well as suitable clinical markers (for both pollutant exposure and oxidative stress) to gain a more accurate assessment of the effectiveness of air quality policies. Further work in identifying susceptible populations is also required. For example, increasing our knowledge of genotype-phenotype associations and inheritable gene-environment interactions involved in the host response to environmental air pollutants will be particularly important. Another, more specific, research direction that requires both epidemiological and mechanistic studies is the way in which air pollutants influence respiratory infections, again especially in particularly vulnerable subgroups of the population.

Success in identifying susceptible subpopulations will be necessary if diagnostic screening and therapies/preventive agents for pollution-induced respiratory diseases are to be developed. Individualised pharmacotherapy with antioxidant (by reducing oxidative stress and/or enhancing antioxidant defences of the human airway) and anti-inflammatory agents, to stem the damaging effects of air pollutants in vulnerable subgroups, may well prove to be an option in our increasingly urbanised world. In addition to focused, high quality research, a cleaner and healthier environment ultimately relies upon collaborative efforts of the government (through legislation and education) and the public (through, for example, responsible use of transportation), and effective translation of the scientific evidence base into risk communication and public policy.

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BRIEF CLINICAL REVIEW: NON-RESPONDING PNEUMONIA

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ABSTRACT

A slowly resolving or non-resolving pneumonia (NRP) is a common clinical dilemma, affecting 10-20% of patients hospitalised with community-acquired pneumonia. Potential causes are many and include inadequate or inappropriate antibiotic therapy, antibiotic resistant pathogens, infectious complications, or incorrect diagnosis. Objective criteria have been described to define clinical stability and represent the best current definition of adequate treatment response. The time to clinical stability varies substantially between patients, being longer in older patients, patients with comorbidities, and patients with a higher severity of pneumonia. NRP is associated with increased mortality and requirement for intensive care unit admission, and so it is essential to identify these patients. Once non-response is recognised, patients should undergo a full re-evaluation, including microbiological testing, repeat chest X-ray and consideration of further imaging, and an increased spectrum of antibiotic therapy if drug resistant pathogens are suspected. A wide range of non-infectious disorders can masquerade as bacterial pneumonia, including pulmonary embolism, malignancy, interstitial lung diseases, alveolar haemorrhage, and vasculitis. There is no uniform recommended diagnostic or treatment approach for patients with NRP. The investigations and interventions required are determined on a case-by-case basis. The present article reviews the causes, investigation, and management of NRP, and presents an algorithm for identification and management of these patients.

Keywords: Pneumonia, antibiotics, biomarkers, severity score.

INTRODUCTION

Community-acquired pneumonia (CAP) is one of the most common acute medical conditions requiring hospitalisation.[1] The majority of hospitalised patients with CAP respond rapidly to antibiotic therapy and follow an uncomplicated course, but a proportion of patients fail to respond to initial therapy and require additional investigation and treatment.[2,3] Despite advances in clinical care, the mortality rate remains 5-15%.[4,5] Patients with non-responding or progressive pneumonia represent a group of patients where appropriate early intervention can improve outcome while preventing overtreatment. This article reviews the definition, causes, investigations, and management of non-responding pneumonia (NRP).

NRP is a common clinical problem that physicians will encounter regularly. The terms NRP and treatment failure are often used interchangeably by investigators, but in reality, are a quite different phenomena. Defining treatment response and non-response have important implications for clinical decision-making, since intravenous (IV) to oral switch, hospital discharge, and treatment escalation will all depend on an accurate assessment of treatment response.[6-10]

Treatment Response and Clinical Stability

Treatment response has traditionally been difficult to define because radiographic changes, which are used to define the presence of pneumonia, can take up to 6 weeks to resolve and often lag behind the clinical recovery of patients.[11] Figure 1 illustrates

the stages of clinical recovery.[12] Microbiological resolution occurs early, with blood cultures and other microbiological samples becoming negative very quickly after commencement of antibiotic therapy. Inflammation then begins to resolve, with a reduction in inflammatory cytokines and biomarkers such as C-reactive protein (CRP).[13] As the systemic inflammation resolves, patient symptoms start to improve until they reach a validated level of clinical symptom recovery known as 'clinical stability'.[14] At this stage, pneumonia is considered to have responded to treatment, and prognosis at this point is excellent, complications are rare, and relapse is unusual.[14-16] Patients may still have radiographic changes and will not feel fully recovered in terms of symptoms and return to usual activities. Indeed, questionnaire studies suggest that a complete return to baseline requires several weeks or even months.[17,18]

The Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) 2007 guidelines recommend the use of Halm's[14] criteria for determining the presence of clinical stability, and therefore, treatment response. These clinical criteria have been extensively validated and are a reliable measure of improvement across different healthcare systems and patient populations. These criteria consist of temperature ≤37.8 °C, heart rate ≤100 beats/minute, respiratory rate ≤24 breaths/minute, systolic blood pressure ≥90 mmHg, O_2 saturation ≥90%, or arterial O_2 tension ≥60 mmHg, normal mental status, and normal oral intake.[14] All of these criteria have to be met for clinical stability to be reached (although allowance is made for the usual functional status of patients, for example chronic obstructive pulmonary disease [COPD] patients with low resting oxygen saturations or patients with chronic cognitive impairment).[6] These criteria have gained widespread acceptance and the time required to achieve these stability criteria is now an FDA recommended end-point for clinical trials in community-acquired bacterial pneumonia.[19] In a prospective study, Aliberti et al.[20] showed that once clinical stability criteria were met (n=410 patients with CAP), the prognosis was excellent, with no in-hospital deaths, no episodes of haemodynamic instability, and only five patients (1.2%) experiencing respiratory complications. Similar results were reported in studies from the UK,[15] US,[13] and Spain.[13]

Alternatives to Halm's clinical stability criteria have been proposed. The simplified ATS criteria were defined in the 2001 ATS guidelines and consist of only four criteria: improvement in cough and shortness of breath, absence of fever >37.8 °C for >8 hours, normalisation of the leukocyte count by 10% from the previous day, and adequate oral intake.[21]

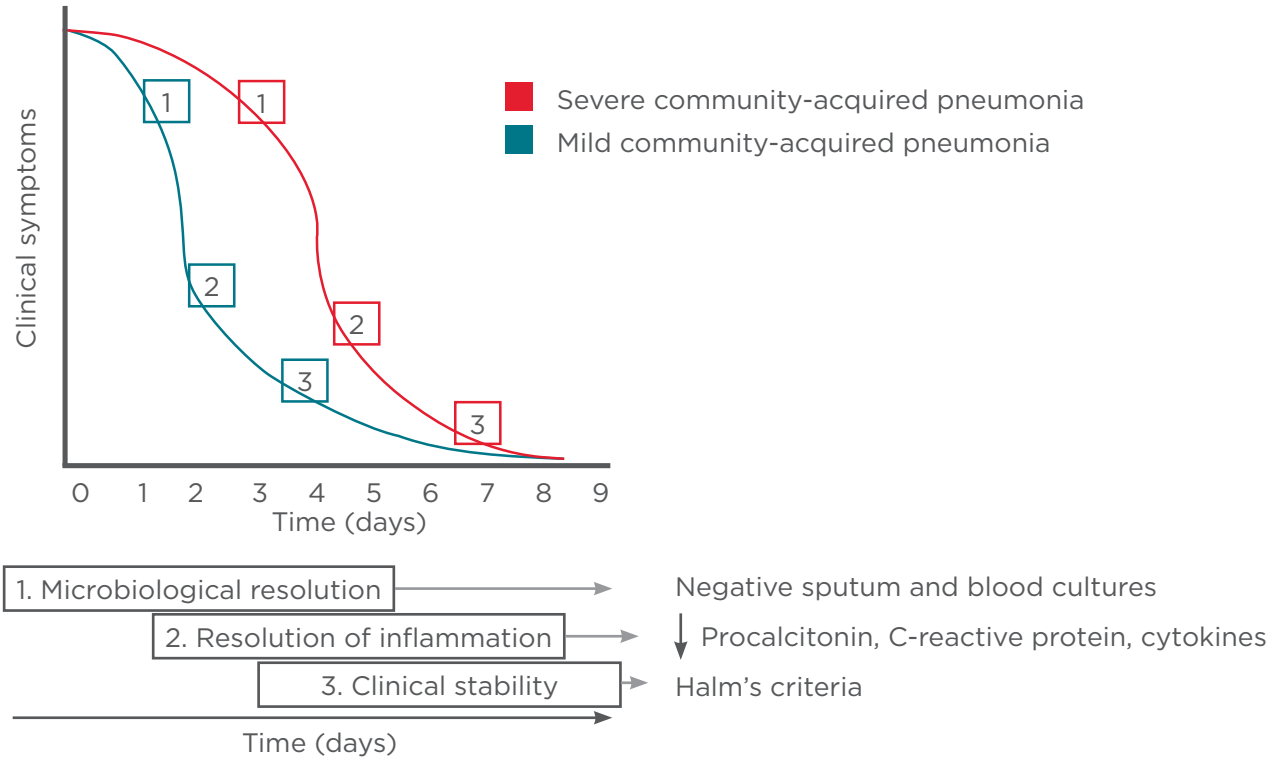

Figure 1: A schematic representation of recovery from community-acquired pneumonia.

Although simple, and therefore easier to implement in clinical practice, these criteria may be less sensitive. In the study described above by Aliberti et al.,[20] four patients who achieved these criteria died (compared to none using Halm's criteria) and the overall complication rate was more than double that seen with Halm's criteria. Akram et al.[15] compared four strategies for determining treatment response: Halm's criteria, the simplified ATS criteria, reduction in the CURB65 score, and CRP reduction. This study found that Halm's criteria was the most effective to define treatment response (0.5% mortality, 0.3% risk of requiring mechanical ventilation or vasopressor support, and 0.7% risk of developing complicated parapneumonic effusion or empyema), although a reduction in CRP was also found to give excellent prediction.[15]

Biomarkers certainly appear promising as a guide to treatment response. Two studies have previously shown that a reduction in CRP by >50% from baseline indicates an excellent prognosis.[13,22] In a prospective study of 570 patients, those achieving a reduction of CRP by ≥50% at day 4 had a mortality rate of 0.5% compared to 18.3% in patients where the CRP failed to fall or rose despite treatment.[22] A Spanish study found a reduction of CRP below 30 mg/L indicated an excellent prognosis. In the Spanish study, CRP <30 mg/L had a positive predictive value for treatment response of 97%, slightly better than procalcitonin.[13] A combination of Halm's criteria and CRP <30 mg/L was 100% specific and had a positive predictive value of 100%, indicating no patients reaching these criteria had complications.[13] Procalcitonin reduction certainly appears to be useful to guide treatment response, as clinical trials have indicated that antibiotic therapy can be stopped once procalcitonin falls below a threshold level (the threshold used is often different depending on the assay or disease under study), without an increase in clinical failure or mortality.[23,24]

Treatment failure and NRP

Treatment failure is defined as persistence or progression of the infection resulting in the requirement for ventilatory support or the development of septic shock.[6] Occurrence within the first 72 hours is referred to as early failure, and after 72 hours as late failure.[25] The distinction is used as it is thought that after 72 hours, late treatment failure is often due to nosocomial complications, while in the first 72 hours it is typically the result of the severity of pneumonia itself. This article will address the situation which is perhaps more difficult to define, the one in which the patient remains unwell for longer than expected, despite apparently appropriate treatment, where they fail to improve, but without clinical deterioration.

The term 'NRP' is not clearly defined. Fein and Feinsilver[26] previously proposed treatment failure as delayed radiographic improvement and deterioration according to worsening of radiographic changes. As previously mentioned, radiographic changes have proven to be relatively insensitive markers of treatment response. Non-response is therefore better accepted as a lack of an adequate clinical response to treatment, and therefore, a failure of the above clinical stability criteria to improve in the expected period of time.

Improvement Rates

Patients will improve at different rates, and perhaps the most frequent cause of 'NRP' is an unrealistic expectation of how quickly patients will achieve clinical stability.[7] The median time to clinical stability in most studies is 3 days; for this reason, the authors recommend a routine re-evaluation of all patients still hospitalised at day 3 to identify patients with NRP.[13-16] The outcome of such a re-evaluation, however, may often be that the patient is progressing at the expected rate and simply requires more time. The most important predictors of delayed time to clinical stability are age, comorbidities, and disease severity. In the study by Akram et al.,[27] there was a direct relationship between the CURB65 score, a validated scoring system for pneumonia severity,[28,29] and time to clinical stability, with patients with low-risk pneumonia (CURB65 0-1) responding in median 2 days, moderate pneumonia (CURB65 2) median 3 days, and patients with severe pneumonia[3-5] requiring 4, 7, and 8 days, respectively.[15] The same pattern is seen with other severity indices.[30]

Other predictors of delayed time to clinical stability in a prospective Spanish study of 1,424 patients included confusion, pleural effusion or multilobar consolidation, COPD, cardiac co-morbidities, and admission to an intensive care unit.[3] Gram-negative pneumonia and pneumonia due to Legionella and Staphylococci are also recognised to be associated with a prolonged recovery.[7] Therefore, it is possible to identify on admission that older patients, patients with extensive radiological findings, chronic co-morbidities, and patients with more severe disease will require more time to respond to treatment. The authors would advocate greater

use of clinical stability criteria in clinical practice, as evidence suggests that the majority rely on clinical judgement. In a European-wide audit (n=2,039 patients with CAP from 10 countries), only 28.7% of respondents used clinical stability criteria in clinical practice.[31]

IMPACT AND CAUSES OF NRP

The lack of a uniform definition of NRP makes estimating the frequency difficult. The frequency of progressive pneumonia (treatment failure) is estimated at 15% of hospitalised patients.[3] If defined as a failure to achieve clinical stability by day 3, the frequency of 'non-responding' pneumonia is as high as 40%.[13-16] The true frequency lies somewhere in between, as not all patients in the latter group truly have NRP, but may progress slowly due to other reasons such as age and comorbidity. Patients failing to improve as expected have a poorer prognosis with an average increased length of stay of 4 days, and an increase in mortality reported as between 15% in those failing to reach clinical stability and 49% in patients with progressive pneumonia.[32,33]

NRP should trigger a complete re-evaluation of the patient, taking into account not only features of the acute infection but also demographic, lifestyle, and microbiological and pharmacological factors. It is essential to avoid assuming the initial diagnostic label was correct as up to 20% of cases of NRP are found to have a non-infective cause for their pulmonary infiltrate - so called 'pneumonia mimics'.[32]

Causes

Despite the above, the most common reasons identified in the literature for NRP are related to infection.[32] Important considerations are pneumonia due to organisms not covered by initial empirical antibiotic therapy, such as multidrug resistant pathogens, atypical pathogens or tuberculosis, or severe infections with a recognised longer response time to treatment, e.g. *Staphylococcus aureus* pneumonia.[6,7]

Table 1: Infections and risk factors associated with non-responding pneumonia.

Risk factor	Possible organism
Comorbidities	
COPD/bronchiectasis[36,37]	*P. aeruginosa*, Enterobacteriaceae
Alcohol abuse[38]	Enterobacteriaceae including *K. pneumoniae*, tuberculosis, anaerobes
Risk factors for aspiration[39]	Enterobacteriaceae, anaerobes
Risk factors for MDR pathogens	
Immunosuppression[40]	Opportunistic pathogens depending on severity of immunosuppression, MRSA, *P. aeruginosa*
Prior hospitalisation, previous antibiotic use, tube feeding, severe functional impairment[41-43]	MRSA, *P. aeruginosa*, Enterobacteriaceae including MDR
Travel	
South Western USA	Coccidioidomycosis
South East Asia	*B. pseudomallei*
Southern Europe	Penicillin/macrolide resistant *S. pneumoniae*
Exposures	
Exposure to birds	*C. psittaci*
Exposure to rabbits	*F. tularensis*
Demographic/lifestyle	
Intravenous drug use	*S. aureus*
Non-pulmonary source for infection	Line sepsis, *C. difficile*, and catheter associated infection

COPD: chronic obstructive pulmonary disease; MDR: multiple drug resistance; MRSA: methicillin-resistant *Staphylococcus aureus*.

The second major classification of infectious causes are infectious complications, most frequently complicated parapneumonic effusion, empyema, and lung abscess.[34,35] These complications are difficult to predict, although risk factors include younger age, IV drug use, low albumin, low serum sodium, thrombocytosis, and the presence of pleuritic chest pain.[34,35] Clinical features are notoriously poor at predicting the aetiology of pneumonia on admission but, in patients with NRP, they may give a clue to underlying aetiology (Table 1).

Non-infectious causes are less frequent than infectious disorders but may still affect >20% of patients with NRP. In one of the most detailed investigations, Arancibia et al.[32] studied 444 patients hospitalised with CAP; 30 patients had NRP and 19 had progressive pneumonia. A cause was identified in 65% of patients, with infection being the most frequent. 23 patients had likely persistence of primary infection, 11 had developed a nosocomial infection, and non-infectious disorders were present in 9 (malignancy, interstitial lung disease, cardiac complications, foreign body).[32] There is a feeling that non-infectious mimics of pneumonia are becoming more common as the population is ageing and becoming more comorbid. These mimics include: pulmonary embolism/pulmonary infarction, pulmonary oedema, lung cancer or metastatic disease, cryptogenic organising pneumonia, diffuse alveolar damage, alveolar haemorrhage, eosinophilic pneumonia, hypersensitivity pneumonitis, drug reaction/drug fever, vasculitis (e.g. Wegener's granulomatosis, Churg-Strauss syndrome), and lipoid pneumonitis. These may be suspected from their individual presenting features or from the results of investigations such as chest X-ray/computed tomography (CT) imaging. In elderly patients, however, the signs and symptoms of pneumonia may be less obvious, making diagnosis difficult based on clinical features alone. A detailed review of the presenting features of these disorders is beyond the scope of this review.

MANAGEMENT APPROACH TO NRP PATIENTS

Investigations

The authors advocate a re-evaluation of patients at day 3 if clinical stability has not been reached and clinical improvement is not satisfactory. Repeat testing of CRP can be useful alongside assessment of the clinical criteria. Repeat physical examination may reveal evidence of a parapneumonic effusion. Consider non-pulmonary sources of infection which may include any organ system, and also consider super-added infections such as line sepsis and *Clostridium difficile* infection which is a common complication of antibiotic therapy in some healthcare systems.[44] Recent data suggest that cardiovascular complications including myocardial infarction (MI) are common in CAP patients and may be under-recognised.[45-48] MI was identified in 20% of patients experiencing clinical deterioration in a retrospective US study (n=500 patients). Although lower rates are reported elsewhere, this is an important consideration.[45-48] Electrocardiography (ECG) should be performed in patients with NRP, even in the absence of chest pain. Left ventricular failure is perhaps the most common pneumonia mimic and is a clinical diagnosis, though this may be supported by echocardiography and measurement of cardiac biomarkers.[49]

Results of microbiological testing should be reviewed, as results from cultures performed on admission and sensitivity testing may only be available at 48-72 hours. Risk factors for unusual or resistant pathogens should be considered, and the appropriateness of the initial empirical antibiotic therapy considered in the context of the current clinical findings and clinical response. Repeat microbiological testing should be considered, particularly in patients that remain febrile or where the microbiological evaluation on admission was incomplete, as is frequently the case in clinical practice. Depending on the radiological and clinical circumstances, additional testing for Mycobacteria, fungi, or other opportunistic pathogens such as *Pneumocystic jirovecii* may be considered, the latter in populations with immunocompromise. In these cases, bronchoscopy is most likely to achieve high quality samples. Use of bronchoscopy and bronchoalveolar lavage is recommended in cases of clinical deterioration or failure to improve where non-invasive microbiological sampling has not been helpful, where opportunistic or unusual pathogens are suspected, and where certain pneumonia mimics are considered, such as endobronchial lung cancer, pulmonary haemorrhage, and acute eosinophilic pneumonia.[6] There are rare cases where lung biopsies, e.g. video-assisted or open lung biopsies, are required.

Repeat chest radiography is recommended in non-responding patients at day 3 and is mandatory in

patients showing any evidence of deterioration. Identification of a pleural effusion should be followed by ultrasound scanning and pleural aspiration to exclude complicated parapneumonic effusion or empyema which require prompt chest drainage.[6,7] After repeat physical examination, blood tests, microbiological evaluation, ECG, and chest radiography, the cause will be obvious in the majority of cases. Conventional or high resolution CT imaging is commonly used and is useful where history or radiological appearances suggest possible malignancy, lung abscess, or interstitial lung disease. Patients with NRP and risk factors for lung malignancy (particularly smoking) should undergo chest CT scanning. CT pulmonary angiogram is important to exclude pulmonary embolism as an alternative diagnosis and should be considered in patients with risk factors. It is important to remember that D-dimer is not helpful in pneumonia patients, as it rises in proportion with the severity of pneumonia.[50] An algorithm for recommended investigations in non-responding patients is shown in Figure 2. As previously mentioned, the differential diagnosis of NRP is wide and no algorithm can satisfactorily capture all possible permutations, but this represents a useful guide. Conversely, in patients responding adequately to treatment, it is possible to recommend IV to oral switch therapy, hospital discharge, and/or short course antibiotic treatment.[8-10,51,52]

Antibiotic Therapy and Corticosteroids

The decision to broaden antibiotic therapy is important, as excessive broad spectrum antibiotic therapy is associated with a higher risk of complications including gastrointestinal side-effects and *Clostridium difficile* infection. The impact of antibiotic related side-effects is often underestimated but the standard regime of beta lactam plus macrolide (the most commonly used worldwide) can be associated with diarrhoea in up to 20% of patients as an example.[52-54] In the case of a patient with NRP, after careful exclusion of alternative diagnoses, escalation of antibiotic therapy should be considered.

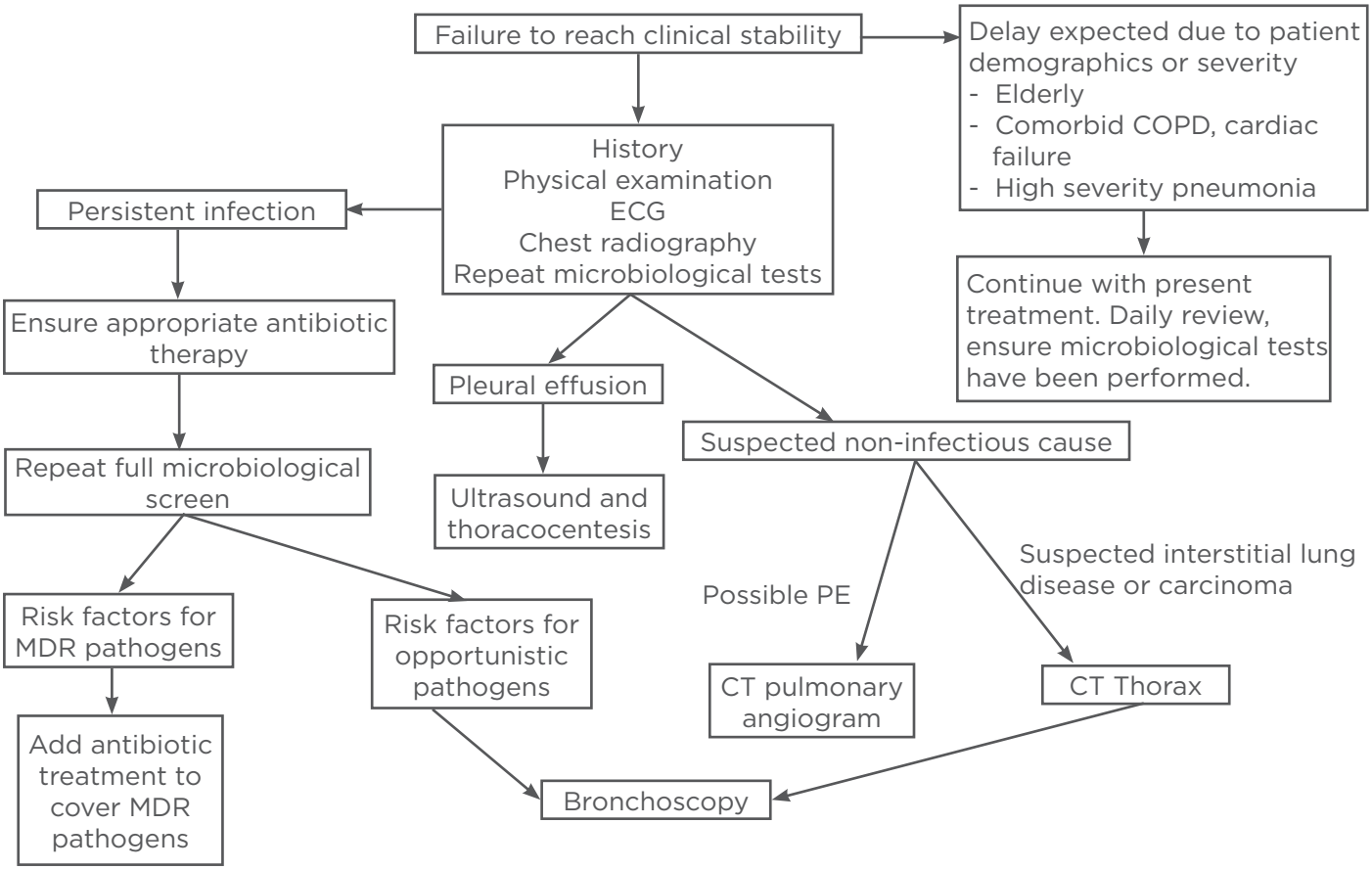

Figure 2: An algorithm for the investigation and management of non-responding pneumonia.
ECG: electrocardiography; MDR: multidrug resistance; COPD: chronic obstructive pulmonary disease; CT: computerised tomography; PE: pleural effusion.

Standard antibiotic therapy varies greatly between different healthcare systems and so no general guidance is possible here. Initial therapy should include coverage of typical organisms (*Streptococcus pneumoniae, Haemophilus influenzae, S. aureus*) and atypical pathogens (*Mycoplasma pneumoniae, Legionella pneumophila, Chlamydophila pneumoniae*).[6,7] This is usually achieved with the combination of a beta-lactam and macrolide or a fluoroquinolone.[6] Therefore, in a patient with NRP - if initial therapy did not include atypical coverage - this should be amended. The most frequent organisms not covered by initial antibiotic therapy include *Pseudomonas aeruginosa*, methicillin-resistant *S. aureus* (MRSA), and resistant Enterobacteriaceae.[40-43] The frequency of these organisms vary substantially, being more common in North America and Asia and less frequent in Northern Europe.[41] In general, therefore, if an infectious cause for non-response is suspected, antibiotic therapy should be escalated to include broader coverage of *P. aeruginosa* and Enterobacteriaceae, plus MRSA in the presence of risk factors or in high prevalence regions.

Although commonly used in clinical practice for patients with NRP, there is no evidence that corticosteroids are beneficial in this context. Several randomised controlled trials of corticosteroid administration on admission have failed to demonstrate benefit, with the exception of one trial in which a 0.5 day shortening of length of stay was reported.[55-58] One small pilot trial of IV dexamethasone in severe patients showed a dramatic reduction in mortality in the steroid arm, but was affected by imbalances between groups at baseline and was prematurely terminated. Therefore, corticosteroids are reserved for cases where a steroid responsive alternative diagnosis is considered, such as crytogenic organising pneumonia or eosinophilic pneumonia.

CONCLUSION

NRP is common, and represents a difficult clinical problem as the cause may vary from a benign delay in recovery to life-threatening progressive pneumonia. A systematic approach to investigation and management is recommended with consideration of both infectious and non-infectious causes.

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Bacteria arming newborns against asthma

INFANTS who are exposed to irritants such as household bacteria, dander, and allergens are less likely to experience allergies, wheezing, and asthma.

Contradicting the instincts of parents everywhere, this news comes from a scientist-led investigation, tracking the health of 467 inner city newborns across America, over the course of 3 years.

Investigators visited the infants' homes to measure levels of present allergens and then tested the babies for allergies and wheezing by implementing blood and skin-prick tests, physical exams, and parental surveys. They further collected the bacterial content of dust from the homes of 104 of the 467 infants for analysis.

"What this tells us is that not only are many of our immune responses shaped in the first year of life, but also that certain bacteria and allergens play an important role in stimulating and training the immune system to behave a certain way."

Dr Robert Wood,
Division of Allergy and Immunology,
Johns Hopkins Children's Center,
Baltimore, USA

Infants who lived in homes containing cat and mouse dander and cockroach droppings during their first year had significantly lower wheezing rates by age 3.

Dr Robert Wood, study author, Chief of Division of Allergy and Immunology, Johns Hopkins Children's Center, Baltimore, Massacusetts, USA, said: "Our study shows that the timing of initial exposure may be critical. What this tells us is that not only are many of our immune responses shaped in the first year of life, but also that certain bacteria and allergens play an important role in stimulating and training the immune system to behave a certain way."

Interestingly, a further finding was uncovered when researchers analysed the effects of increasing exposure to allergens: 41% of children who were allergy and wheeze-free had grown up in environments containing the widest variety of bacterial species, whereas only 8% of children who developed both allergies and wheezing were exposed to toxins during their first year; thus, the protective effects of exposure do not appear to be valid after the age of 1.

Researchers say that these findings could help to inform preventive strategies for allergies and wheezing, both of which lead to asthma - a disease that affects 1.1 million children in the UK and 7 million children in the USA today.

Hsp90 inhibitors used to predict who will benefit from lung cancer treatment

"This study is a positive step forward in making sure lung cancer patients get the most effective treatment based on the genetic mistakes that underpin their disease."

Dr Emma Smith,
Senior Science Information Officer,
Cancer Research UK

UNRAVELLING the structure of an abnormal protein that can cause anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer, which is particularly aggressive, may help to predict which patients will benefit from treatment.

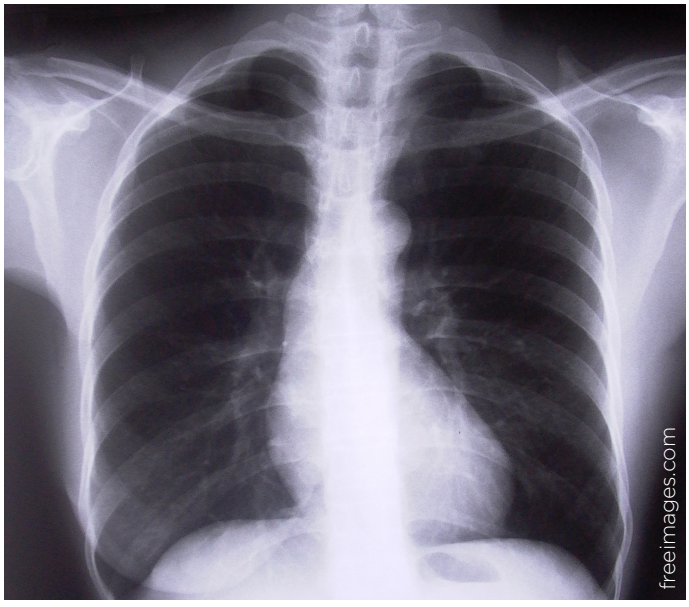
The findings of a new study will enable doctors to identify patients who carry the abnormal protein, and thus, would benefit from the specific lung cancer treatment, sparing them from unnecessary adverse effects.

In ALK, which is accountable for 4% of all cases, two different genes become locked together forming an enhanced version of a protein. This protein enables the cancer to grow and spread rapidly, but if this protein is blocked it could prevent growth and thus kill the cancer.

To assess the shape of this protein an X-ray crystallography was used. It was discovered that, depending on where the gene had fused, different shapes were visible. It also revealed that some shapes needed an additional protein to work.

The researchers hypothesised that if this supporting protein was blocked using Hsp90 inhibitors, the enhanced proteins would no longer work and the cancer cells would die. To test this theory, cells were grown in a lab and the findings revealed that Hsp90 inhibitors were able to kill cells where the unstable protein was present; this was in stark contrast to cells containing the stable protein.

Dr Emma Smith, Senior Science Information Officer, Cancer Research UK, said: "This study is a positive step forward in making sure lung cancer patients get the most effective treatment based on the genetic mistakes that underpin their disease. We now need to build on this research and gather further clinical data to confirm these findings. It may lead to doctors developing a simple genetic test to spot patients who will benefit from a drug targeted against their disease, and spare patients (unlikely to benefit) from unnecessary side-effects."



App breathes life into fight against pneumonia

"With this app, we can give healthcare workers with few resources faster and more accurate measurements, help them make better decisions, and give them more time with their patients."

Dr Walter Karlen, Anaesthesia Pharmacology and Therapeutics, Child and Family Research Institute, Vancouver, Canada

CHILDREN suffering from pneumonia and other respiratory diseases may benefit from a new mobile app which can measure respiratory rates approximately 6-times faster than standard clinical methods.

RRate, developed by researchers at the Child and Family Research Institute (CFRI) at BC Children's Hospital and the University of Columbia, New York City, New York, USA, can reliably measure a child's breathing rate at an average of 9.9 seconds. This is considerably quicker than the current practice in which healthcare workers count a patient's breaths for 60 seconds, aided by a stopwatch.

Instead, RRate allows for practitioners to measure respiratory rates by tapping the touch screen of a phone, upon every inhalation. As well as calculating the breaths of an infant during a given time, the app also provides an animation of a breathing baby, which allows for a direct contrast with the breathing patient, and a free version of the device is now available online.

This simple yet innovative technology is a great step towards more accurate diagnoses for children who suffer respiratory illnesses such as pneumonia - the biggest cause of death in children worldwide - and allows for quicker intervention with antibiotics, providing the potential to save thousands of lives.

"Mobile phones are changing how we administer healthcare, especially in rural settings and developing countries where access to medical devices is limited," commented Dr Walter Karlen, research co-leader and Postdoctoral Fellow, Anaesthesia Pharmacology and Therapeutics, CFRI, Vancouver, British Columbia, Canada. "With this app, we can give healthcare workers with few resources faster and more accurate measurements, help them make better decisions, and give them more time with their patients."

RRate researchers now seek to further improve diagnoses of pneumonia in low-resource settings by combining the app with the Phone Oximeter, which provides non-invasive measurements of blood oxygen levels using a mobile phone and light sensor.

Anoro®: combating symptoms of COPD

"We are delighted by today's marketing authorisation for Anoro Ellipta which provides a new alternative for COPD patients for whom dual bronchodilator treatment in a single inhaler may be appropriate."

Mr Darrell Baker, Senior Vice President and Head of GSK Global Respiratory Franchise, London, UK

ANORO®, used for treating patients with chronic obstructive pulmonary disease (COPD), which is believed to affect 4-10% of the adult population, has recently been granted marketing authorisation by the European Commission, which will come as welcome news to many sufferers nationwide.

COPD obstructs airflow and interferes with an individual's breathing. Anoro is a daily maintenance bronchodilator treatment which relieves adult patients of COPD symptoms. A combined remedy, its ingredients include two bronchodilators, umeclidinium (UMEC) and vilanterol (VI), within a single inhaler, and is now licensed across 31 European countries, as well as the USA, and Canada.

The treatment was tested in eight Phase III clinical trials, where 1,296 of 6,000 COPD patients received the recommended dose of UMEC/VI once-daily, and it was revealed to be successful at relieving symptoms.

A Summary of Product Characteristics uncovered important safety information regarding the inhaler's use in patients who suffer additional medical conditions.

The treatment is unsuitable for anyone experiencing asthma or acute episodes of bronchospasm and may produce paradoxical bronchospasm, which can be life-threatening. Additionally, cardiovascular effects may be seen after the administration of UMEC/VI, so the treatment should be used with caution in patients who suffer from cardiovascular disease; full details of prescribing information are available online.

Just how Anoro can benefit COPD patients was summarised by Mr Darrell Baker, Senior Vice President and Head of GlaxoSmithKline (GSK) Global Respiratory Franchise, London, UK, who commented: "There are many people across Europe living with COPD who experience a variety of symptoms and for whom the disease represents a significant burden. GSK is committed to developing a range of new therapeutic options that provide physicians with treatment choices when considering individual patient needs.

"We are delighted by today's marketing authorisation for Anoro Ellipta which provides a new alternative for COPD patients for whom dual bronchodilator treatment in a single inhaler may be appropriate."

Feeling stressed?

Just breathe, Spire can help

TRACKING breathing through a device known as Spire can provide insight into emotions and state of mind. Monitoring accurate respiration may help to solve issues such as asthma and chronic obstructive pulmonary disease.

According to the World Health Organization, respiratory illnesses are the third leading cause of deaths globally. It is hoped that this device will be able to offer valuable insights into acute health implications for conditions such as stress.

"When you are not thinking about it, the signal is constantly changing; you are holding your breath, changing the inhalation-exhalation rates, changing all these things that we see correlate to these different states of mind. You can consciously control these, and by extending your exhale you are telling your body that you are in a relaxed state, you are in a safe place so it can lower cortisol levels and increase endorphins," said Mr Jonathan Palley, Co-Founder and Chief Executive Officer, Spire Inc., San Francisco, California, USA.

When under stress, the body releases hormones, increases both heart and breathing rates, and narrows the blood vessels. If in this state for too long, emotional and physical damage can occur. Additionally, breathing can also influence involuntary bodily responses, but controlling our breathing allows us to control our heart rate, blood pressure, and circulation.

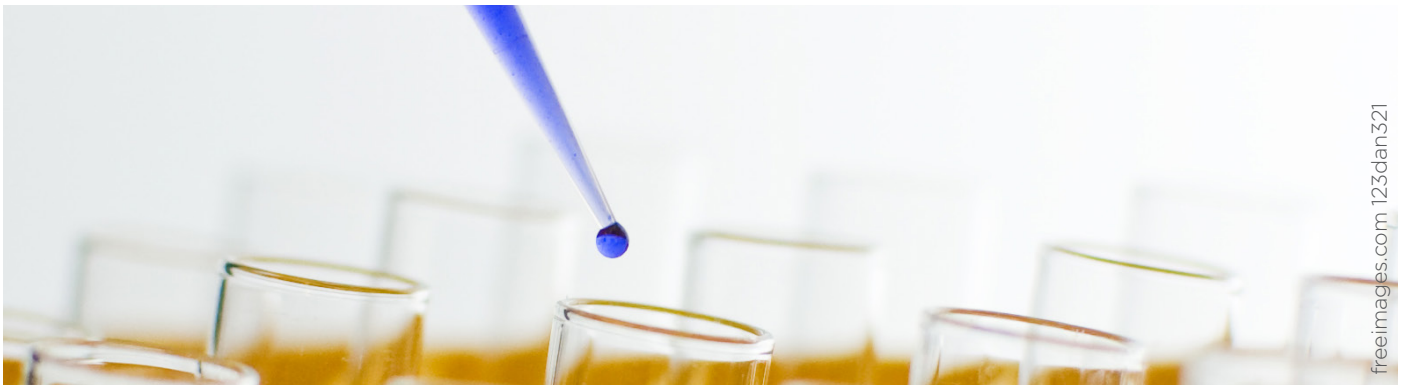
The device monitors the wearer's breath and notifies them when they are becoming stressed or unfocused. This notification helps the wearer to lower stress. Moreover, the device offers an opportunity to carry out a breathing exercise.

The device monitors the wearer's breath and notifies them when they are becoming stressed or unfocused.

In a pilot study the results indicated that 70% of participants felt significantly more focused and less tired while using Spire after a couple of weeks.

Gathering this vast amount of data through monitoring breathing may have important clinical implications in the future. To assess the full worth of the device, pilot studies are being planned.

New drug has potential to combat inflammatory diseases



Two studies have already proved the adequacy of the drug's basic active ingredient, and now researchers are working to improve its methods of application.

SCIENTISTS are collaborating to develop pharmaceuticals which can combat chronic inflammatory diseases (CIDs). CIDs can affect numerous organs and body parts, stemming from a malfunction of immunological processes.

There is a huge market for these products as statistics indicate that 300 million asthma sufferers, 600 million pneumonia patients, and up to 30% of individuals contend with allergic rhinitis worldwide.

A versatile new drug by Nuvo Research Inc., already approved for use in several countries, has been found to assist in the process of wound healing, and is further warranted as a means of treating various chronic diseases; scientists are now establishing just how the substance works.

Prof Jürgen Arnhold, Professor of Medicine, Institute of Medical Physics and Biophysics, University of Leipzig, Leipzig, Germany, said: "Inflammation is the body's emergency response, but inflammation normally begins to abate the moment it starts. In order for the organism to calm back down and stabilise, the immune system is temporarily suppressed. The body supresses its defence mechanisms until the inflamed tissue has managed to regain its normal functions. This regenerative process is disrupted in the case of chronic inflammation."

Various complications can occur during this healing process; if these complications are allowed to develop beyond a certain mark, the patient's immune system will violently react. It is precisely this interplay between immunosuppression and immunological overreaction that scientists are investigating.

In order for the drug to be approved in Europe, investigations are now being conducted into its safety and effectiveness using mice. Focusing on three major respiratory conditions, scientists have to establish 20 model systems with which they can simulate various aspects of inflammatory diseases, enabling them to record the effects of administering variable doses.

Two studies have already proved the adequacy of the drug's basic active ingredient, and now researchers are working to improve its methods of application; one future hope is that it will be available for administration by family doctors.

Belt-busting bellies boost COPD risk

Women with a waist size of ≥43 inches and men with a waist size of ≥46 inches showed a 72% increased risk of developing lung disease.

OBESITY has been postulated as a factor for increased risk of chronic obstructive pulmonary disease (COPD), otherwise known as emphysema and chronic bronchitis, which is currently the third leading cause of death in the USA.

A study, led by researcher Dr Gundula Behrens, Department of Epidemiology and Preventive Medicine, University of Regensburg, Regensburg, Germany, began in 1995 and followed over 113,000 Americans between the ages of 50 and 70.

Participants did not have COPD, cancer, or heart disease when the investigation commenced, yet after 10 years of follow-up, over 3,600 subjects had developed COPD, and it appeared that waist size was a strong predictor of COPD risk, regardless of whether the individual had ever smoked or not.

Investigators also found that women with a waist size of ≥43 inches and men with a waist size of ≥46 inches showed a 72% increased risk of developing lung disease; those who were physically active five times or more per week had a 29% decreased risk of COPD, compared with others who were physically inactive.

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Perhaps contradictorily, subjects who were underweight also had an increased risk of COPD (56%). According to investigators, this may have been due to malnutrition and reduced muscle mass or inflammation, which reduces the ability of the lungs to self-heal.

Dr Norman Edelman, Senior Medical Consultant, American Lung Association, Chicago, Illinois, USA, commented: "At this point, I think it's possible that it is just an association without causal effect."

However, he added: "The link between association is that both COPD and obesity cause shortness of breath," and for an individual who is both obese and a smoker, the risk of developing COPD is significantly heightened.

Veiled threat of oxygen therapy demands consumer care

RATIONAL use of oxygen therapy is vital for the safe and effective treatment of respiratory illness, but toxicity is possible through excess administration.

There may be a misconception that oxygen therapy is harmless as we all breathe oxygen constantly. However, artificial oxygen application is a prescription drug and must not be associated with the oxygen we breathe naturally; a doctor's prescription is required for safe and effective treatment.

If the saturation level of oxygen in a patient's body drops due to a specific respiratory illness or injury, oxygen therapy becomes necessary in the artificial restoration and optimum maintenance of this level. This method of tackling 'respiratory failure' is outlined by Dr Girija Nair, Head Department of Pulmonary Medicine, Dr DY Patil Medical College, Mumbai, India.

Oxygen therapy enhances gas exchange until lung functions improve, with targets set at ≥60 mm Hg and ≥90 mm Hg for pressure (PaO_2) and saturation pressure (SpO_2). Care must be taken to avoid excess supply, with oxygen toxicity occurring when oxygen concentration exceeds 50% across a treatment duration of >48 hours. Symptoms of oxygen toxicity are non-productive cough, nausea and vomiting, and sub-sternal and chest pain, while suppression of ventilation can result in increased carbon dioxide and its associated narcosis.

Examples of oxygen dispensing devices include piped-in oxygen cylinders, which can supply oxygen for up to 57 hours at the required regulated flow, and concentrators, which have molecular sieves delivering 90% oxygen. Oxygen delivery devices need oxygen supply, flowmeter, oxygen tubing, delivery device, and humidifier.

A clear indication is needed for oxygen therapy and the type of treatment required. Doctors must outline the purpose of the therapy, demonstrate the procedure, and also list potential complications. Prescriptions must discuss the air flow rate, delivery system, duration, and instructions for monitoring, while patient evaluation is essential.

Artificial oxygen application is a prescription drug and must not be associated with the oxygen we breathe naturally; a doctor's prescription is required for safe and effective treatment.

Lack of knowledge and action underline COPD concern

"It is important that physicians develop an individualised approach that works best for each patient."

Prof Meilan Han,
Division of Pulmonary and Critical Care,
University of Michigan,
Ann Arbor, USA

ENHANCED education and improved dialogue with physicians may be the key to effective management of chronic obstructive pulmonary disease (COPD), and potentially fatal complications known as exacerbations (flare-ups), in patients.

"Exacerbations can have a devastating impact on overall health, and they can actually cause COPD to progress even faster and reduce lung function," said Mr Scott Cerreta, Director of Education, COPD Foundation, Flagstaff, Arizona, USA. "Developing an action plan with instructions to help patients - and their caregivers - identify warning signs and what steps to take if an exacerbation should occur is a critical part of managing COPD."

Of all the COPD patients who enrolled in the two-part national COPE (Chronic Obstructive Pulmonary Experience) survey initiative, launched by the COPD Foundation, 62% said that they did not know much about COPD exacerbations, while an extra 16% did not know what an exacerbation was. 60% of subjects said that they lacked an action plan to tackle a flare-up. Conversely, the arm of the survey which questioned physicians revealed that 98% and 92% reported exacerbation discussion and action plan establishment with their patients, respectively, highlighting the need for improved physician-patient communication concerning COPD.

COPD symptoms were experienced for an average of 2 years and 9 months pre-diagnosis in surveyed patients, a dangerous statistic considering that early detection and proper diagnosis of COPD are paramount in managing this disease while slowing its progress.

"COPD can be treated, but it is crucial for doctors to diagnose it early and for patients to follow the appropriate therapeutic strategies to improve symptoms, increase activity, and reduce the chances of exacerbations," said Prof Meilan Han, Associate Professor of Medicine, Division of Pulmonary and Critical Care, University of Michigan, Ann Arbor, Michigan, USA. "It is important that physicians develop an individualised approach that works best for each patient."

Featured Suppliers

Respiratory

Responsible for the development of some of the world's most important drug products in fields ranging from diabetes care to veterinary medicines, Bayer HealthCare is a key innovator in the manufacturing of pharmaceutical and medical products. The Bayer subdivision's aim is to create state-of-the-art, groundbreaking products to improve the lives of patients worldwide. It aims to accomplish this through its consumer care, medical innovations, and pharmaceutical divisions, addressing some of the great challenges in the modern era. The company has bases in 5 continents, with approximately 55,300 people working for the subgroup in over 100 countries.

Boehringer Ingelheim (BI) is a group of companies heavily focused on the research, development, manufacturing, and marketing of potentially life-altering pharmaceuticals. The group has over 46,000 employees and 140 affiliated companies distributed worldwide. BI has made clear its vision of 'value through innovation', which is also central to the company's corporate strategy. By carrying out key research projects in the development of innovative drugs, the company has a strong focus in the main therapeutic areas of cardiovascular diseases, respiratory diseases, diseases of the central nervous system, metabolic diseases, virological diseases, and oncology.

Novartis AG has one outstanding mission: to discover, design, and deliver cutting edge healthcare to patients worldwide. Founded in 1996 and based in Basel, Switzerland, this world-leading pharmaceutical company has consistently produced medical breakthroughs, developing innovative products for patients and consumers. A host of innovative pharmaceuticals, generics, vaccines, and consumer health products have provided pain relief and boosted patient quality of life since the company's inception. Operating in 140 countries, the seismic ambitions of Novartis have attracted a total of 135,000 associates, including top experts in research and development.

PneumRx Inc. is a Californian-based medical device start-up that focuses on making solutions with minimal invasiveness, designed to fulfil unmet medical needs in pulmonary medicine. The company's signature product - the RePneu® lung volume reduction coil - was made to overcome the key challenges in emphysema management. The coil itself was made to cause a reduction in lung volume and to restore elastic recoil in order to improve lung function, exercise capacity, and quality of life for patients with emphysema. Patients tend to recover gradually in their pulmonary function and physical endurance over several months, which allows them to continue enjoying daily activities.

ResMed is a global leader in the development, manufacturing, and marketing of a range of innovative medical products, which aim to treat and manage a plethora of respiratory disorders; the target conditions involve sleep-disordered breathing. ResMed was founded in 1989 and sells a wide range of products in over 70 countries worldwide. The company is committed to advancing innovative technology in sleep and respiratory medicine and to commercialising these innovative products, while incorporating these technologies on a global level. ResMed always treats its employees and patients with the utmost professionalism, regardless of the project scale.

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Respiratory

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Contemporary Management of Neonatal Pulmonary Disorders

6th-7th November 2014

Arizona, USA

This conference has attracted an impressive guest faculty who are renowned national researchers and teachers in newborn pulmonary medicine. The event is targeted towards neonatologists, fellows, nurse practitioners, and respiratory therapists. The conference is unique in that there will be numerous opportunities during the panel discussion, evening reception, or one of the conference breaks to interact informally with members of the faculty.

American College of Allergy, Asthma and Immunology (ACAAI) Annual Meeting 2014

6th-11th November 2014

Atlanta, USA

This meeting is the premier event in the field of allergy and immunology. Allergists, internists, paediatricians, and other healthcare professionals will be in attendance. The educational scientific programme will be delivered by internationally recognised scientists, and will include a wide range of clinical conferences, symposia, workshops, presentations, and state-of-the-art lectures. The event will also provide ample scientific networking opportunities.

British Thoracic Society (BTS) - Occupational and Environmental Lung Disease 2014

7th November 2014

Sheffield, United Kingdom

This educational course will be delivered by a faculty of experts and aimed at respiratory specialist registrars, newly qualified consultants, and other healthcare professionals. The meeting will focus on the causes and pathophysiology of acute and chronic occupational and environmental lung diseases. The management of occupational and environmental lung disease, particularly the importance of early diagnosis and exposure avoidance, will be discussed.

9th International Respiratory Syncytial Virus Symposium (RSV)

9th-13th November 2014

Stellenbosch, South Africa

The theme of the symposium is 'RSV: A global health problem' and brings to attention the problem of RSV in both industrialised and developing countries. The programme will cover a broad range of topics such as RSV in children, adults, and immune-compromised patients. The aim of the event is to get an extensive overview of the recent advancements in the entire field of RSV, including epidemiology, pathogenesis, molecular biology, and vaccines.

British Thoracic Society (BTS) - Thoracic Ultrasound Course

17th November 2014

Newcastle upon Tyne, United Kingdom

This informative course aims to educate the participants with the principles of thoracic ultrasound and on safe practice. This course will also focus on understanding the indications, limitations, and common pitfalls of thoracic ultrasound. There will be practical sessions which will allow delegates to familiarise themselves with the basic techniques. This course is aimed at consultants, technicians, and trainees in respiratory medicine.

European Respiratory Society (ERS) - Non-invasive ventilation (NIV): Basic Concepts Course

20th-21st November 2014

Hanover, Germany

This course provides participants with an overview of the basic technical skills and clinical information to enable safe use of NIV. NIV has been increasingly used in recent years, both in acute and long-term settings. Participants will be able to treat patients of mild-to-moderate severity in varying settings. The target audience who would benefit from this course include pulmonologists, intensivists, physicians, and physiotherapists.

14th Central European Lung Cancer Conference (CELCC) 2014

29th November-2nd December 2014

Vienna, Austria

This multidisciplinary conference will focus on both educational and scientific developments in the field of lung cancer. There will be a wide range of symposia, oral sessions, poster sessions, and satellite symposia. Primary prevention and screening in Central Europe will be important topics along with molecular diagnosis, immunotherapy, and predictive biomarkers. Recent advances in the diagnosis and treatment of lung cancer will be updated.

World Allergy Organisation (WAO) International Scientific Conference

6th-9th December 2014

Rio de Janeiro, Brazil

The theme of the conference is: 'Advancing the borders of allergy: From treatment to prevention by targeting the environment, infections and the susceptible patient.' There will be a stimulating and varied scientific programme, highly relevant to both the theory and practice of allergy, asthma, and clinical immunology. This will provide a forum for the most useful combination of latest research, review of practices, and problem-based learning.