OVERVIEW

This year’s American Thoracic Society International Conference, ATS 2010, was held at the Ernest N. Morial Convention Center in New Orleans, from 14 to 19 May. The event attracted thousands of delegates from all over the world, including respiratory specialists, primary care physicians, other healthcare professionals and representatives from the pharmaceutical industry. The extensive programme was varied and covered the most up-to-date information on treatment options for a range of respiratory diseases. In this ATS 2010 report, we focus on highlights from oral sessions and posters on treating Chronic Obstructive Pulmonary Disease (COPD).

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What should we treat?

‘Exacerbations are costly, and are most costly to the patient’ (A. Punturieri, USA)

The ATS 2010 annual conference left delegates in no doubt over the global impact of COPD and the challenge of effective disease management. The issue was illustrated well by a poster describing the burden of COPD on healthcare resources in 10 hospitals throughout Canada. (Chapman et al, 2010) The study revealed that COPD was a more common cause for hospitalisation than myocardial infarction (MI) or pneumonia, and was the most common cause for admission in community-based hospitals. The mean length of stay was 11±2 days, at an estimated cost of over $10,000 per patient.

Many hospitalisations of patients with COPD are, of course, associated with acute exacerbations. Recent research adds to the growing evidence that exacerbations severely impact patient health. New data show that the risk of MI and stroke is greatly increased in the 5 days following an exacerbation (Donaldson et al, 2010), and that lung function, quality of life and mortality increases with the frequency of exacerbations. (Decramer et al, 2010) Data from ECLIPSE*, a 3-year observational study of the natural history of COPD, show that 14.5% of patients with COPD experienced one or more severe exacerbations in the first year of observation, and that this was associated with increased depression and fatigue, and poor quality of life. (Anzueto et al, 2010)

Several sessions at ATS 2010 included discussion of how best to reduce the frequency and severity of exacerbations, widely accepted as a major goal of COPD therapy. Recognising the huge impact of exacerbations, the National Institutes of Health (NIH) has funded the COPD Clinical Research Network (CCRN), a programme of clinical trials with the express aim of finding treatments that will achieve this goal, of reducing the frequency and severity of exacerbations. (www.copdcrn.org)

A number of presentations described COPD as a multicomponent disease that is associated with numerous systemic comorbidities. Chronic inflammation is known to contribute to development of conditions such as type 2 diabetes, osteoporosis and cardiovascular disease (CVD), and may explain why they are often found in association with COPD.

The prevalence of comorbidities is high in patients with COPD, and appears to increase according to COPD severity (Figure 1). (Regan et al, 2010; Black-Shinn et al, 2010) Citing brand new data published by Alvar Agusti’s group, Dr Donald Sin from Vancouver told the audience that 1 in 3 patients with coronary artery disease had airflow limitation when assessed by spirometry. (Soriano et al, 2010) The lung disease was undiagnosed in 60% of these patients. Conversely, Silver et al described their findings that over half of patients hospitalised for COPD exacerbations had hypertension, one third had diabetes or ischaemic heart disease and one quarter had congestive heart failure. (Silver et al, 2010)

*ECLIPSE: Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints

Figure 1. Percentage of patients with COPD and osteoporosis or CVD in the COPDGene Study. (Adapted from Regan et al, 2010; Black-Shinn et al, 2010) The presence of comorbidities often indicates a poor prognosis for patients with COPD, and can present limitations to
Key points

COPD is a major cause of hospitalisation and healthcare expenditure all over the world

- Reducing the severity and frequency of exacerbations is a major goal of COPD management
- Patients with COPD frequently have comorbidities such as CVD
- Growing evidence supports a link between the chronic inflammation that underlies COPD and its comorbidities

References


COPD Clinical Research Network. Available at: http://www.copdcrn.org


Current treatments for COPD

‘Current treatments are good...but we can do better’ (G. Criner, USA)

Four large scale clinical trials (TORCH, INSPIRE, OPTIMAL, UPLIFT*) have demonstrated significant benefits associated with inhaled bronchodilators in patients with COPD. However, as Dr Gerard Criner from Philadelphia pointed out in one of the ATS 2010 oral sessions, approximately 60% of patients in these trials continued to experience exacerbations, despite receiving the best available COPD therapies. This observation elegantly highlights the need for new COPD treatments, particularly those that will reduce the impact of exacerbations when added to existing treatments.

**GOLD standard?**

In one of ATS 2010’s lively debate sessions, a packed theatre enjoyed the exchange between Dr Sonya Buist (Portland, OR) and Dr Dirkje Postma (Netherlands) on whether ‘GOLD is leading to optimal COPD management’. Dr Buist argued that since its inception in 2000, the Global strategy for the diagnosis, management, and prevention of COPD from Global Initiative for Chronic Obstructive Lung Disease (GOLD) has raised awareness of COPD, increased its diagnosis and management through spirometry testing, and stimulated research in the field.

In rebuttal, Dr Postma argued that FEV1-based spirometry, upon which GOLD staging and treatment recommendations are based, prevents optimal management of the disease. She highlighted that patients who exacerbate frequently are classified as ‘severe’ or ‘very severe’ using the GOLD approach. Many studies, however, suggest that frequent exacerbators can have lung function in the ‘moderate’ range (Figure 2). In support of Dr Postma’s argument, a poster by Kim et al reported that among 2,500 patients in the COPDGene Study, those with chronic bronchitis had significantly more frequent and more severe exacerbations than patients without these symptoms, even though both groups had similar FEV1 levels.


Under the current classification system, frequent exacerbators at more moderate stages of the disease are not recommended certain medications vital for the successful management of exacerbations, suggesting that guidelines may need to take into account overall symptomology rather than focusing on spirometric measures.

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**Stage I: Mild**
- FEV1/FVC < 0.70
- FEV1 = 80% predicted
- Active reduction of risk factor(s): influenza vaccination
- Add short-acting bronchodilator (when needed)
- Add regular treatment with one or more long-acting bronchodilators (when needed); Add rehabilitation
- Add inhaled glucocorticosteroids if repeated exacerbations
- Consider surgical procedures

**Stage II: Moderate**
- FEV1/FVC < 0.70
- 50% ≤ FEV1 < 80% predicted
- Add long-term oxygen if chronic respiratory failure

**Stage III: Severe**
- FEV1/FVC < 0.70
- 30% ≤ FEV1 < 50% predicted
- Add long-term oxygen if chronic respiratory failure

**Stage IV: Very Severe**
- FEV1/FVC < 0.70
- FEV1 < 30% predicted or FEV1 < 50% plus chronic respiratory failure

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References


www.goldcopd.com

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*TORCH: Towards a Revolution in COPD Health; INSPIRE: Investigating New Standards for Phrophylaxis in Reduction of Exacerbations; OPTIMAL: Optimal Therapy of Chronic Obstructive Pulmonary Disease To Prevent Exacerbations and Improve Quality of Life; UPLIFT: Understanding Potential Long-Term Impacts on Function with Tiotropium
Bronchodilators and CVD risk – the evidence

There were many discussions about the properties of existing drugs for COPD, particularly using data from the landmark UPLIFT* and TORCH* trials on tiotropium and salmeterol/fluticasone, respectively. In one interesting session, Professor Donald Tashkin from UCLA addressed the controversial argument that certain bronchodilators can negatively affect a patient’s risk of CVD. He concluded that, after reviewing data on approximately 20,000 patients enrolled in large randomised clinical trials, there is no evidence to support this hypothesis. On the contrary, recent data indicate that tiotropium appears to lower CV risk (Celli et al, 2010).

Key points

• Treatment guidelines may need to evolve to recognise the effects of overall symptoms on disease severity rather than focusing on FEV₁

• Current treatments for COPD relieve breathlessness, improve lung function and reduce exacerbations

• Recent data support a cardioprotective effect of long-acting bronchodilators such as tiotropium

• While current treatments for COPD offer many benefits, patients continue to experience symptoms and exacerbations, indicating the need for new treatments
Emerging therapies

‘Preventing even one exacerbation is important’ (N. Hanania, USA)

ATS 2010 reminded those in the field of respiratory medicine that despite the widespread benefits of currently available treatments, there is still an urgent need for new treatments for COPD. Several presentations and poster sessions highlighted a number of promising new pipeline products for the treatment of COPD. These included new products in the long-acting muscarinic antagonist (LAMA) and long-acting β2-agonist (LABA) classes, as well as novel approaches to treatment such as macrolides, statins and anti-inflammatories. Data from clinical studies on two products – roflumilast and indacaterol – appeared to dominate the poster sessions.

Roflumilast
Roflumilast is an anti-inflammatory agent belonging to a second generation of phosphodiesterase 4 (PDE4) inhibitors. It is currently in development as an add-on therapy to first-line maintenance treatment for patients with severe COPD (post-bronchodilator FEV1 <50% predicted) associated with chronic bronchitis and a history of frequent exacerbations. Roflumilast was shown to significantly reduce exacerbations and improve lung function in primary phase III clinical trial data published in 2009. A number of posters at ATS 2010 presented further analyses of these data, providing interesting insights into the efficacy and safety of roflumilast.

Many patients with advanced COPD continue to experience exacerbations despite being treated with first-line maintenance treatments. A poster by Hanania and colleagues demonstrated that addition of roflumilast to LABA therapy significantly reduced the risk of exacerbations by approximately 20%, on top of that achieved by LABAs alone. (Hanania et al, 2010) This pre-specified sub-group analysis of two replicate 12-month studies (Calverley et al, 2009) confirmed the additive efficacy of roflumilast for patients who have symptoms of chronic bronchitis, are already using first-line maintenance treatment for COPD, and who have a history of frequent exacerbations. It also showed that the efficacy of roflumilast was independent of previous inhaled corticosteroid use, prior to randomisation.

In further analyses of the two replicate 12-month clinical studies, (Calverley et al, 2009) Martinez and colleagues found that most of the 2.17kg mean weight loss associated with roflumilast treatment in the phase III clinical studies occurred within the first 6 months of treatment. (Calverley et al, 2009) The vast majority of patients who reported weight loss and participated in a post-trial follow-up study regained weight following cessation of roflumilast, indicating that the weight loss was transient and reversible. (Martinez et al, 2010) In addition, bio-impedance data showed that the weight loss in roflumilast-treated patients was primarily due to a reduction in fat mass. (Wouters et al 2010)

Together, these new data showed that roflumilast provides additive efficacy in for patients with COPD associated with chronic bronchitis who are already using first-line maintenance treatment for COPD and who have a history of frequent exacerbations. The data also provide further insights into the weight loss observed in some roflumilast-treated patients.

Indacaterol
Indacaterol, a new once-daily LABA, was recently approved for the treatment of COPD in Europe and other countries. Pooled data from phase III clinical trials showed that indacaterol improves health-related quality of life compared with other LABAs or placebo (Siler et al, 2010; Kleerup et al, 2010) and exercise endurance. (O’Donnell et al, 2010) Moreover, indacaterol significantly improved lung function irrespective of patient baseline characteristics including age (Mahler et al, 2010), concomitant use of inhaled corticosteroids (Donohue et al, 2010), or demonstrated reversibility to short-acting bronchodilators. (Kleerup et al, 2010)

These data indicate improved efficacy of indacaterol over currently available LABAs in patients with moderate-to-severe COPD.
Key points

• Numerous pharmaceutical products are being tested in clinical trials for the treatment of COPD

• Roflumilast is a once-daily oral anti-inflammatory that is in late-stage development for the treatment of severe COPD in patients with cough and sputum and a history of frequent exacerbations, that reduces exacerbations and improves lung function

• Indacaterol is a recently-approved once-daily LABA that has demonstrated improved efficacy over other currently available LABAs
Future therapeutic targets

‘COPD is a disease of inflam-aging’ (A. Agusti, Spain)

The mechanisms underlying COPD hold the key to future therapeutic approaches. ATS 2010 made a strong case for two major mechanistic pathways – chronic inflammation and accelerated aging. There was no one specific session devoted to the role of chronic inflammation in COPD, but this theme permeated most of the COPD presentations. In particular, many of the inflammatory processes that underlie COPD also contribute to a number of comorbidities associated with COPD.

As part of CCRN – the NIH-funded research programme that aims to find treatments to reduce exacerbations – the STATCOPE Study* is investigating the effects of simvastatin on exacerbation rate in patients with COPD, at doses that reduce inflammation. (www.copdcrn.org)

Several speakers made the case that COPD is a disease characterised by accelerated aging of the lung (Figure 3). (Ito and Barnes 2009) Citing data from the 4-year UPLIFT* trial, Professor Bartolome Celli from Italy observed that the distribution of patients among GOLD stages is the same regardless of age. This suggests that some patients experience rapid decline in lung function, which may be due to accelerated aging of the lung.

A number of signalling pathways that are involved in aging were discussed at ATS 2010. Of note, Professor Peter Barnes from London explained how the protein SIRT1 plays a central role in the development of chronic inflammatory diseases such as COPD and its comorbidities. Suppression of SIRT by oxidative stress promotes chronic inflammation (in COPD, diabetes and metabolic syndrome), degradation of elastin (in atherosclerosis, emphysema, hypertension and skin wrinkling) and oxidative stress (in accelerated aging). (Nakamaru et al, 2009) Sirtuin activators are found naturally in plants, such as resveratrol which is abundant in red wine. However these molecules have low bioavailability, so synthetic SIRT agonists are in development and have demonstrated protective effects against smoke inhalation in mice.

In other areas, the ongoing MACRO Study is investigating the effects of a macrolide antibiotic, azithromycin, on the frequency of exacerbations. (www.copdcrn.org) Since many exacerbations are associated with bacterial infections, prophylactic use of antibiotics is a logical approach to prevention, although it carries a risk of antibiotic resistance. Use of inhaled, rather than systemic, antibiotics is a novel therapeutic approach that was discussed in an evening symposium (sponsored by Bayer Healthcare).

Key points

- Anti-inflammatory and anti-aging pathways offer many potential targets for new COPD treatments
- Key targets include:
  - Anti-inflammatory agents
  - Statins
  - Sirtuin activators
  - Prophylactic antibiotics

*STATCOPE: Statins in COPD Exacerbations; UPLIFT: Understanding Potential Long-Term Impacts on Function with Tiotropium

References
