Research Highlights

Highlights from the latest articles in chronic obstructive pulmonary disease

New therapies for chronic obstructive pulmonary disease

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Evaluation of: Hansel TT, Barnes PJ: New drugs for exacerbations of chronic obstructive pulmonary disease. *Lancet* 374, 744–755 (2009); Bourbeau J, Johnson M: New and controversial therapies for chronic obstructive pulmonary disease. *Proc. Am. Thor. Soc.* 6, 553–554 (2009).

Chronic obstructive pulmonary disease (COPD) is a clinical syndrome characterized by airflow limitation that is not fully reversible, and a complex inflammatory process that involves inflammatory cells such as neutrophils, $CD8^+$ T cells, macrophages and eosinophils and mediators, enzymes, cytokines and so on.

Treatment of COPD typically consists of smoking cessation and promotion of a healthy lifestyle, including physical exercise or rehabilitation on the one hand, and drug treatment with bronchodilators and anti-inflammatory drugs (mainly inhaled corticosteroids) on the other hand. Unfortunately, effects of currently used drugs in reducing symptoms and the number and severity of exacerbations, improving lung function, quality of life and survival are limited, and effective new drugs to treat COPD, preferably oral drugs that really moderate and reduce inflammation, are eagerly awaited.

In Hansel and Barnes [1] and Bourbeau and Johnson [2], a comprehensive summary is provided on developments in drug therapy that may potentially add to out current options for medical treatment of COPD.

In the paper by Hansel and Barnes, they highlight the importance of acute exacerbations of COPD, both for individual patients and for society. Inhaled bronchodilators, both β-agonists and antimuscarinic drugs, will remain the mainstay of management to reduce symptoms and to improve lung function. Modifications of existing drugs will become available that may act longer or faster. Antibiotics, oral steroids,noninvasive ventilation and early pulmonary rehabilitation will help recovery and prevent recurrences. The authors state that there is a need for new drugs to inhibit corticosteroid-insensitive neutrophil inflammation, both in stable disease and to prevent and treat exacerbations without increasing the risk of infection by blunting host defense mechanisms. Phosphodiesterase inhibitors, chemokine receptor antagonists, cytokine-directed therapy and drugs to modify oxidative stress are currently being tested. Statins may decrease systemic inflammations and have been shown to increase survival in patients with COPD, and may help to reduce exacerbations, although prospective studies are not yet available. New approaches directed against the innate immune system may emerge, but are still far from being introduced.

For the treatment of stable COPD, the nonpharmacologic management, including self-management support to adopt and maintain a healthy lifestyle, remains of pivotal importance. This means a shift from management by the healthcare provider to management by the patient themself. More research is needed to test specific components of self-management in patients, taking into account the many phenotypes of COPD that we have learned to recognize in recent years, including COPD in never-smokers, the chronic bronchitis versus the emphysema phenotype, underweight and obesity and the many forms of co-morbidities that COPD patients tend to suffer from.

Bibliography

1 Hansel TT, Barnes PJ: New drugs for exacerbations of chronic obstructive pulmonary disease. *Lancet* 374, 744–755 (2009).

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Phosphodiesterase-4 inhibition in chronic obstructive pulmonary disease

Evaluation of: Calverley PM, Rabe KF, Goehring UM *et al.*: Roflumilast in symptomatic chronic obstructive pulmonary disease: two randomised clinical trials. *Lancet* 374, 685–694 (2009);
Fabbri LM, Calverley PM, Izquierdo-Alonso JL *et al.*: Roflumilast in moderate-to-severe chronic obstructive pulmonary disease treated with long-acting bronchodilators: two randomised clinical trials. *Lancet* 374, 695–703 (2009).

Phosphodiesterases (PDEs) are a superfamily of enzymes that activate the intracellular second messengers cAMP and cGMP, and drugs that inhibit PDEs, especially PDE4, have been shown to have a wide range of anti-inflammatory actions *in vivo* and *in vitro.* PDE4 inhibitors provide inhibition of chemotaxis, leukocyte activation and cytokine production.

Some of these selective PDE4 inhibitors are currently being tested in Phase III clinical trials. In the August 29, 2009 issue of the *Lancet*, which was devoted to COPD, two papers reported a total of four clinical trials with roflumilast, a second-generation PDE4 inhibitor with acceptable tolerability in preclinical and clinical studies with COPD patients.

In the two placebo-controlled, double-blind, multicenter studies by Calverley *et al.* [1], roflumilast 500 µg once per day for 1 year was tested in outpatients with severe airflow obstruction, bronchitic symptoms and a history of exacerbations. Primary end points were the change in pre-bronchodilator forced expiratory volume in one second (FEV_1) and the rate of moderate and severe exacerbations. In total, 3091 patients were included, many of whom appeared to be undertreated, as no more that 50% were taking inhaled long-acting β-agonists (LABA), and only little over 40% used inhaled corticosteroids (ICS). Patients using LABA were allowed to continue using that drug, but both long-acting antimuscarinic drugs (tiotropium) and ICS were not allowed for the duration of the study. Roflumilast was found to reduce the number of exacerbations. The estimated rate of exacerbations per patient per year that were moderate or severe was 17% lower in the roflumilast group than in the placebo group. The time to first exacerbation was prolonged in the roflumilast group by a mean of 9 days (71 vs 80 days). The time to a second moderate or severe exacerbation was prolonged by 29 days (177 vs 148 days). The difference in prebronchodilator FEV_1 was 48 ml in favor of the roflumilast group. After 1 year, the prebronchodilator forced vital capacity (FVC) in the roflumilast group was increased by 64 ml, whereas in the placebo group, prebronchodilator FVC was -34 ml after 1 year.

Side effects were similar to those reported from earlier studies. These included weight loss (by a mean of 2.1 kg in the roflumilast group), diarrhea and nausea. Most side effects occurred in the first 4–12 weeks of treatment, and resulted in more patients withdrawing in the first 12 weeks of the study in the roflumilast group. From their study, the authors conclude that roflumilast reduced exacerbation frequency and improved FEV_1, irrespective of concomitant use of LABA or smoking status.

The second paper published in the same issue of the *Lancet* reported on two double-blind multicenter studies of roflumilast 400 mg once per day or placebo added to either salmeterol 50 µg twice-daily or tiotropium 18 µg once-daily in outpatients with moderate-to-severe COPD [2]. The primary end point was the change in prebronchodilator FEV_1 after 24 weeks of treatment. A number of relevant secondary end points were evaluated, including dyspnea questionnaires and exacerbation rate. Again, inhaled corticosteroids were not allowed throughout the study. In both trials lung function (pre- and post-bronchodilator FEV_1 and FVC) was found to be significantly better in the roflumilast-treated patients. Effects on symptoms were variable, and due to side effects more patients dropped out in the roflumilast groups than in the placebo groups. In general, roflumilast did better when added to tiotropium than when added to salmeterol, both in terms of improvements in lung function and in patient-reported outcomes. The authors conclude that roflumilast maintains its clinical efficacy in patients with moderate-to-severe COPD who are already treated with inhaled long-acting bronchodilators, a setting which is likely to reflect clinical practice when the drug will eventually be introduced. However, this comes with some adverse effects that may result in discontinuation in the first few months after initiation of the drug.

When compared with the effects of inhaled steroids that were seen in clinical trials in patients with more or less similar disease severity, effects of roflumilast on lung function are comparable. Whether roflumilast will be equally effective in COPD patients already on ICS, as most patients currently appear to be, remains to be established.

In their thoughtful editorial comments on both these reports, O'Byrne and Gauvreau [3] state that roflumilast is beneficial in patients with COPD, especially when added to long-acting bronchodilators. However, a number of issues remain to be resolved before selective PDE4 inhibitors such as roflumilast can become standard therapy in COPD. The studies reported here were in selected patient phenotypes with symptoms of bronchitis and exacerbations, who appeared to be undertreated by current standards. The clinical relevance of the improvements in lung function that were seen is not clear, side effects remain significant and information on effects of PDE4 inhibitors in patients who are treated with ICS is lacking. Roflumilast,

being an anti-inflammatory agent, reduced exacerbation frequency, but so do inhaled steroids and long-acting bronchodilators, and with each drug added to an existing regime, additional benefits are likely to decrease. Finally, a study comparing a selective PDE4 inhibitor with the nonselective phosphodiesterase inhibitor theofyllin in a head-to-head manner assessing both effectiveness and toxicity should be available before selective inhibitors find their way to the clinic.

Bibliography

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3 O'Byrne PM, Gauvreau G: Phosphodiesterase-4 inhibition in COPD. *Lancet* 374, 695–703 (2009).

Disease management in chronic obstructive pulmonary disease

Evaluation of: Chavannes NH, Grijsen M, van den Akker M *et al.*: Integrated disease management improves one-year quality of life in primary care COPD patients: a controlled clinical trial. *Prim. Care Respir. J.* 18, 171–176 (2009).

Drug therapy may be one important aspect of the treatment and management of COPD, but nonmedical interventions including smoking cessation and promoting physical activity are equally or even more important, as has been shown in long-term studies in recent years.

In the controlled trial by Chavannes *et al.* [1], an integrated disease management program consisting of optimal medication, reactivation, education and exacerbation management during 1 year in symptomatic primary care COPD patients was compared with usual care. End points were quality of life measured with the St George's Respiratory Questionnaire (SGRQ), the Clinical COPD Questionnaire (CCQ) and the Medical Research Council (MRC) Dyspnea Score. Two primary healthcare centers serving two separate villages in the southern part of the Netherlands were recruited. In one center a team was created comprising two specialized physiotherapists, a respiratory nurse, a dietician, a pharmacist, a supervising primary care physician and a logistical manager. A standardized written protocol allowing for optimally tailored management of all included patients was used. The program included optimal medication prescribing according to current guidelines and adherence monitoring, rapid action plans for exacerbations, personalized physical activity training programs (at least three sessions of at least 40 min of physical activity per week over 3 months) and continuous self-management education, including personal goal-setting by motivational interviewing techniques.

A total of 162 patients were included, 79 of whom were in the intervention group. Unfortunately, results of long function testing were only available for 106 patients. In all other patients, a diagnosis of COPD had been made on clinical grounds. Of the 106 patients with spirometry, 61% had global initiative for chronic obstructive lung disease (GOLD) stage 2 COPD, 10% had stage 1, 25% stage 3 and 3% stage 4 COPD.

After 1 year, the proportion of patients in the intervention group with MRC dyspnea scores greater than two had decreased from 36 to 13%, whereas the number increased from 32 to 44% in the control group. Statistically significant and clinically relevant improvements in SGRC and CCQ scores were seen in the intervention group. No changes were seen in the patients receiving usual care.

From their findings, the authors conclude that an integrated disease management program can improve quality of life in COPD patients treated in primary care. Improvements were greatest in patients with an FEV1:FVC ratio of less than 0.7, and MRC dyspnea scores greater than two. Given the lack of capacity and the high costs of formal rehabilitation programs, they recommend setting up disease management programs in primary care as an effective means of early intervention in COPD.

Bibliography

1 Chavannes NH, Grijsen M, van den Akker M *et al.*: Integrated disease management improves one-year quality of life in primary care COPD patients: a controlled clinical trial. *Prim. Care Respir. J.* 18, 171–176 (2009).

Efficacy of tiotropium in chronic obstructive pulmonary disease

Evaluation of: Tashkin DP, Celli B, Kesten S *et al.*: Long-term efficacy of tiotropium in relation to smoking status in the UPLIFT trial. *Eur. Respir. J.* (2009) (Epub ahead of print).

Long-acting β-agonists and long-acting antimuscarinic agents have become cornerstones in the treatment of symptomatic COPD. Large multicenter trials using these drugs have shown significant effects on symptoms, lung function, quality of life and the rate of exacerbations. Apart from specific inclusion and exclusion criteria and lung function measures such as FEV_1, in most trials no attempts were made to distinguish between different phenotypes of COPD. One relevant phenotypic characteristic is the smoking status in established COPD. Understanding Potential Long-term Improvements in Function with Tiotropium (UPLIFT), a 4-year landmark trial of tiotropium in COPD, allowed for assessment of the influence of smoking status on long-term responses to maintenance bronchodilator therapy [1]. This trial used lung function and patient-reported outcomes including symptoms, exacerbation rate and severity and quality of life as end points. Of the 5993 patients included in the trial, initially 70% of the patients were ex-smokers, and 30% were current smokers. Over the course of the study, after all participants had underwent a smoking cessation program, 14% were continuing smokers, 60% had quit smoking and 26% continued to smoke intermittently. As could be expected, during the trial smokers showed the most rapid decline in FEV_1 (-51 ± 4 ml/year in the abstract, 52 ± 4 ml/year in Table 2 in the paper) and ex-smokers showed the slowest rate of decline in FEV_1 (23 ± 2 ml/year). No differences in the rate of decline in FEV_1 were seen between tiotropium and placebo. Significant improvements in FEV_1, FVC and slow vital capacity (SVC) were seen throughout the trial within each of the three smoking behavior categories. The improvements in the current smokers were numerically larger than in former or intermittent smokers.

Tiotropium was associated with a reduced risk of a first exacerbation in current (by 19%) and in ex-smokers (by 14%), with more or less similar reductions in the number of hospital admissions. Tiotropium was also associated with a tendency towards reduced exacerbation frequency irrespective of smoking status. Tiotropium was associated with improved quality of life scores, albeit not in intermittent smokers, with the effects being largest in current smokers. Continuing smokers exhibited a higher all-cause mortality rate than intermittent or ex-smokers. Tiotropium was associated with significantly reduced mortality in the ex-smokers, but not in continuing smokers. One of the drawbacks of this analysis is that concomitant therapy with inhaled steroids may have influenced responses to tiotropium in different ways in the three patient groups. It is known that the response to inhaled steroids is blunted in smoking asthmatics compared with nonsmokers. So far, such differences in response to inhaled steroids in COPD have not been reported. From their analysis, the authors conclude that tiotropium was associated with improved outcomes in terms of lung function. However, tiotropium had no discernible association with lung function decline in any smoking subgroup, as the rate of decline was similar in the tiotropium- and the placebo-treated patients. FEV_1 dropped fastest in current smokers. Tiotropium was associated with reductions in the risk for and frequency of exacerbations across all smoking categories, which was significant in the ex-smokers, and with statistically significant improvements in health-related quality of life and a significant reduction in all-cause mortality in patients who reported to have given up smoking. The findings of the UPLIFT trial again show that current drug therapy will at most improve symptoms, quality of life, lung function and exercise tolerance in COPD. These are important outcomes in any patient, justifying the ample use of both bronchodilators and inhaled steroids in symptomatic patients with moderate-to-severe COPD. In order to improve survival, however, none of the currently available drugs for the treatment of COPD has been shown to be effective, and this is not likely to change for the years to come. Smoking cessation and physical exercise in any patients, and long-term oxygen therapy and lung volume reduction surgery in highly selected patients, are the only really effective interventions to improve survival.

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