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Abstract: Large clinical trials in chronic obstructive pulmonary disease (COPD) are analyzed and discussed. Unfortunately, all of them have failed to reach their primary endpoint, which has mainly been the effect on the rate of decline in mean FEV_1 (forced expiratory volume in 1 second). Nonetheless, almost all trials have demonstrated benefits in important outcomes such as exacerbation frequency, symptoms, quality of life and other measures of health status, which are arguably more meaningful to individual patients than FEV_1 *per se*.

Keywords: COPD, clinical trials, formoterol salmeterol, tiotropium, budesonide, fluticasone

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Introduction

The increased burden of chronic obstructive pulmonary disease (COPD) [Rabe *et al*. 2007] and the many difficulties in developing new drugs for this disease [Barnes, 2008] have encouraged us to investigate how to improve the use of currently available drugs. In order to do this, large and long-lasting clinical trials have been designed that have explored the capacity of individual therapeutic options to influence the natural history of COPD and, in particular, their impact on some of the most important outcomes of the disease. The need to explore the impact of treatments on individual specific outcomes arises from the fact that COPD is a multicomponent disease characterized by bronchoconstriction, airway and systemic inflammation, structural changes (airway remodeling, emphysema) and mucociliary dysfunction [Rabe *et al*. 2007].

Traditional COPD therapies have focused on symptom control and aim to alleviate the problems of reduced airflow and declining lung function [Rabe *et al*. 2007]. As the symptoms of COPD reflect the multicomponent nature of the disease, the existing therapeutic approach is to target both the symptoms and the inflammation that underlies and drives COPD [Rabe *et al*. 2007].

The first large clinical trials in COPD

Unfortunately, clinical trials with a truly large population of COPD patients and lasting at least 2 years are scarce, although their number has increased in recent years. The duration of trials is a crucial point. The recent recommendations of the ATS/ERS Task Force [Cazzola *et al*. 2008] suggest that pharmacological trials in stable COPD should be ≥ 6 months in order to examine potential outcomes or support claims of treatment response, particularly for regulatory submissions. However, due to seasonal variation, an evaluation of exacerbation frequency requires a period of ≥ 1 year and, in any case, the timing of the study treatment may prove important (e.g. capturing the winter cold season in the majority of patients). Nonetheless, COPD progresses slowly and variably and is often diagnosed relatively late in its course [Rennard and Vestbo, 2008a]. Declining lung function over time is an important component in understanding the natural history of COPD and pharmacological interventions have the potential to alter this trend, although individual patients may have a great deal of variability in their lung function decline over time.

The original Lung Health Study (LHS-1) was the first large and long-term trial in COPD (Table 1). It was a 5-year randomized clinical trial of smoking cessation and regular administration of an inhaled bronchodilator (ipratropium bromide, a short-acting antimuscarinic agent) [Anthonisen *et al*. 1994]. Participants in the two smoking intervention groups, who were suffering from relatively mild COPD, showed significantly

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Table 1. The first large clinical trials.

Trial	Treatment arms and duration	Number of subjects	Trial design	Key endpoints	Major results
LHS-1	(1) smoking intervention plus ipratropium 40 μg three times daily, smoking intervention plus placebo, or no intervention [usual care]; 5 years.	5887 patients (mean postbronchodilator FEV_1: 78% ± 9 of the predicted value).	Open, randomized placebo-controlled parallel-group trial.	Rate of change and cumulative change in FEV_1.	Smaller declines in FEV_1 in participants in the two smoking intervention groups. Small noncumulative benefit associated with use of ipratropium vanished after its discontinuation at the end of the study.
CCLS	Budesonide 800 μg plus 400 μg daily for 6 months followed by 400 μg bid for 30 months, or placebo; 36 months.	290 patients (mean FEV_1: 76% ± 18 of the predicted value).	Double-blind, randomized placebo-controlled parallel-group trial.	Rate of FEV_1 decline.	No effect of budesonide on rate of decline in lung function.
EUROSCOP	Budesonide, 400 μg bid; 36 months.	1277 patients (mean FEV_1: 73% ± 13 of the predicted value).	Double-blind, randomized placebo-controlled parallel-group trial.	Rate of FEV_1 decline.	Use of budesonide associated with a small one-time (first 6 months) improvement in lung function but without appreciably effect on the long-term progressive decline. Possibly more pronounced effect in the subgroup of those who had smoked less.
ISOLDE	Fluticasone 500 μg bid or placebo; 36 months.	751 patients (mean FEV_1: 49% ± 14 of the predicted value).	Double blind, placebo controlled study.	Rate of FEV_1 decline after bronchodilator, changes in health status, frequency of exacerbations, respiratory withdrawals.	No significant difference in the annual rate of decline in FEV_1 ($P = 0.16$). Mean FEV_1 after bronchodilator significantly higher throughout the study with fluticasone compared with placebo ($P < 0.001$). Median exacerbation rate reduced by 25% with fluticasone compared with placebo ($P = 0.026$). Health status deteriorated by 3.2 units a year on placebo and 2.0 units a year on fluticasone ($P = 0.0043$). Withdrawals because of respiratory disease higher in the placebo group (25% *versus* 19%, $P = 0.034$).
LHS-2	Triamcinolone 600 μg bid or placebo; 40 months.	1116 patients (mean FEV_1: 67% ± 13 of the predicted value).	Double-blind, randomized placebo-controlled parallel-group trial.	Rate of FEV_1 decline after the administration of a bronchodilator, respiratory symptoms, cause-specific morbidity and mortality, airway reactivity in response to methacholine, and health-related quality of life.	No significant difference in the annual rate of decline in FEV_1 ($P = 0.34$) but less severe airway reactivity ($P = 0.02$) and reduced dyspnoea ($P = 0.02$) with triamcinolone. Triamcinolone use associated with loss of bone mineral density and increased skin bruising.

(Continued)

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Table 1. Continued.

Trial	Treatment arms and duration	Number of subjects	Trial design	Key endpoints	Major results
BRONCUS	Oral N-acetylcysteine 600 mg per day or placebo; 36 months.	523 patients (mean FEV_1: 57% ± 9 of the predicted value).	Double-blind, randomized placebo-controlled parallel-group trial.	Yearly reduction in FEV_1 and the number of exacerbations per year.	No effect of N acetylcysteine on rate of FEV_1 or VC decline, exacerbation rate, or health status. N acetylcysteine might reduce exacerbation rate in patients not taking inhaled steroids.

smaller declines in FEV_1 (forced expiratory volume in 1 second) than those in the control group. Most of this difference occurred during the first year following entry into the study and was attributable to smoking cessation, with those who achieved sustained smoking cessation experiencing the largest benefit. The small non-cumulative benefit associated with use of the active bronchodilator vanished after the bronchodilator was discontinued at the end of the study. The LHS-1 researchers reported some extensions of the initial trial. Changes in FEV_1 in response to isoproterenol was measured in, 4194 participants in the LHS annually for 5 years, and again 11 years after study entry [Anthonisen *et al.* 2005a]. It was found that large bronchodilator responses were uncommon, but response tended to increase over time. Response was increased more in people who stopped smoking than in those who did not. There was no relationship between bronchodilator response and subsequent rate of decline in pulmonary function. From the original sample of mild COPD participants, 731 patients died (33% of lung cancer, 22% of cardiovascular disease, 7.8% of respiratory disease other than cancer, and 2.3% of unknown causes) after a 14-year follow-up [Anthonisen *et al.* 2005b]. There were differences in mortality in the LHS usual care group compared with the smoking intervention group. Death rates for both lung cancer and cardiovascular disease were greater when rates were analyzed by smoking habit.

Considering that COPD is a preventable and treatable inflammatory disease [Rabe *et al.* 2007; Celli and MacNee, 2004], efforts have also been made to understand if a long-lasting anti-inflammatory treatment is able to change the course of COPD. Four large and long-term trials in COPD, the Copenhagen City Lung Study (CCLS) [Vestbo *et al.* 1999], the European Respiratory Society Study on Chronic Obstructive Pulmonary Disease (EUROSCOP) [Pauwels *et al.* 1999], the Inhaled Steroids in Obstructive Lung Disease in Europe (ISOLDE) [Burge *et al.* 2000], and the Lung Health Study-2 (LHS-2) [Lung Health Study Research Group, 2000], examined only the impact of inhaled corticosteroids (ICSs) (Table 1). A pooled analysis of these studies and other three shorter-term studies indicates that ICSs are likely to be effective in reducing all-cause mortality in stable COPD [Sin *et al.* 2005]. In the first 6 months of treatment, ICS therapy is more effective in ex-smokers than in current smokers with COPD in improving lung function, and women may have a larger response to ICSs than men [Soriano *et al.* 2007]. However, it seems that after 6 months, ICS therapy does not modify the decline in FEV_1 among those who completed these randomized clinical trials [Soriano *et al.* 2007]. It not surprising, therefore, that by following up ISOLDE participants up to 13 years after randomization, it has been documented that their survival is poor (44%) with no differences in total mortality among the participants randomized to ICS or placebo, and that respiratory-related deaths were the most frequent causes of death in these moderate-to-severe COPD patients [Bale *et al.* 2008]. Nonetheless, it must be mentioned that a *post hoc* analysis of the EUROSCOP trial supports the hypothesis that treatment with ICSs reduces ischemic cardiac events in patients with mild COPD [Löfdahl *et al.* 2007]. This is an intriguing finding that suggests that ICSs may reduce systemic inflammation in patients with COPD.

Considering that (1) oxidative stress is of major importance in the pathogenesis of COPD because it is crucial to the inflammatory response

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(through the activation of redox-sensitive transcription factors and pro-inflammatory signaling pathways), and (2) antioxidants such as N-acetylcysteine (NAC) could well reduce oxidative stress [Rahman, 2008], the Bronchitis Randomized on NAC study (BRONCUS) was designed as a randomized placebo-controlled trial of the effects of 600 mg daily NAC on the progression of disease and exacerbation rate in 523 patients with COPD who had frequent exacerbations [Decramer *et al*. 2005] (Table 1). Patients were followed for 3 years. NAC did not affect the rate of decline in FEV_1 or vital capacity (VC), exacerbation rate, or health status. However, subgroup analysis suggested that NAC might reduce exacerbation rate in patients not taking ICSs. Moreover, secondary analysis of functional residual capacity (FRC) data suggested that NAC might reduce hyperinflation.

The three recent fundamental trials

It has been mentioned that the aim of treatment in COPD is to target both symptoms and inflammation. While ICSs are employed to reduce inflammation in more severe patients, their role as standalone medication in COPD is not well defined. However, increasing evidence suggests that long-acting ß$_2$-agonists (LABAs) and ICSs have complementary and synergistic effects when delivered as combination therapy from a single inhaler. Consequently, it is not surprising that other trials have explored the impact of combination therapy with LABAs. In effect, 1-year studies investigating the effect of a combination of LABA and ICS documented that such a combination improves and sustains lung function to significantly greater levels compared with their component drugs, decreases the rate of exacerbations, improves health status and decreases dyspnoea [Calverley *et al*. 2003a, 2003b; Szafranski *et al*. 2003].

The TORCH (Towards a Revolution in COPD Health) study [Calverley *et al*. 2007] is the first large trial that has examined the long-term effect of an active therapy in COPD (Table 2). It was designed and powered to investigate the effect of 3 years' treatment with salmeterol/fluticasone combination (SFC), salmeterol, fluticasone or placebo on all-cause mortality as the primary outcome. The difference in mortality rates narrowly failed to reach statistical significance (hazard ratio 0.825; $p = 0.052$), although treatment was associated with a lower risk of dying than placebo; the respective mortality rates were 12.6% and 15.2%, giving an absolute risk reduction in all-cause mortality of 2.6%. The risk of mortality was significantly lower with SFC treatment compared with fluticasone ($p = 0.007$), but not compared with salmeterol ($p = 0.481$). In any case, data from the TORCH study on secondary outcomes are consistent with and extend previous observations in studies using combinations of LABA plus ICS [Calverley *et al*. 2003a; 2003b; Szafranski *et al*. 2003] in showing that the combination regimen reduced exacerbations significantly, as compared with placebo, including those exacerbations requiring hospitalization. The combination regimen was also significantly better than each of its components alone in preventing exacerbations, and these benefits were accompanied by sustained improvements in health status and FEV_1; the values for both were better at the end of the trial than at baseline. An important safety finding was the excess of patients who received a diagnosis of pneumonia among those receiving study medications containing ICS. Intriguingly, a *post hoc* analysis of the TORCH study showed that pharmacotherapy with SFC, or either component alone, had been able to reduce the rate of decline of FEV_1, thus slowing disease progression [Celli *et al*. 2008].

A large (1323 patients with severe COPD) 2-year, double-blind, double-dummy parallel trial, the INSPIRE (Investigating New Standards for Prophylaxis in Reducing Exacerbations) study [Wedzicha *et al*. 2008], has compared the effect of SFC and tiotropium on the prevention of exacerbations in COPD (Table 2). The results did not show a difference between the two treatment arms for the primary endpoint, but other outcome measures favored the SFC treatment. One of these was the withdrawal rate, which might suggest that SFC better prevented the clinical deterioration that often leads to withdrawal. Another was the difference in the treatment that the exacerbations required. Oral corticosteroids were used more often to treat the tiotropium group, whereas patients on SFC required antibiotics more frequently. It must be highlighted that in this study patients were given prednisolone 30 mg daily for 14 days to 'standardize their COPD management before randomization'. Furthermore, in the INSPIRE study the proportion of patients previously taking ICS was 50%. Interestingly, the dropout rate was similar in the two arms of the study in patients without prior use of ICS (106/339 *versus* 113/325

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Table 2. The three recent fundamental trials.

Trial	Treatment arms and duration	Number of subjects	Trial design	Key endpoints	Major results
TORCH	Salmeterol 50 μg plus fluticasone 500 μg (SFC), placebo, salmeterol alone, or fluticasone propionate alone bid; 3 years	6112 patients; (mean post-bronchodilator FEV_1: 44% of the predicted value).	Randomized, double-blind, parallel group, placebo-controlled trial.	Death from any cause for the comparison between the combination regimen and placebo, the frequency of exacerbations, health status, and spirometric values.	Reduction in death from all causes in SFC group *versus* placebo not statistically significant ($p = 0.052$). Reduced annual rate of exacerbations improved health status and spirometric values in SFC compared with placebo ($p < 0.001$ for all comparisons). Health status and spirometric measurements in SFC group significantly better than in the groups receiving salmeterol alone, or fluticasone alone.
INSPIRE	Salmeterol 50 μg plus 500 μg (SFC) bid or tiotropium bromide 18 μg once daily; 2 years.	1323 patients (mean post-bronchodilator FEV_1: 39% of the predicted value).	Randomized, double-blind, double-dummy, parallel group trial.	Health care utilization exacerbation rate, health status, mortality, adverse events, study withdrawal.	No difference in the overall rate of exacerbations between treatment groups. Treatment with SFC associated with better health status, fewer patient withdrawals, and a lower mortality rate than with tiotropium. small but significant increase in reported pneumonia in the SFC-treated group.
UPLIFT	Tiotropium 18 μg or a matching placebo once daily; 4 years. All respiratory medications, except other inhaled anticholinergic drugs, permitted during the trial.	5993 patients (mean post-bronchodilator FEV_1: 48% of the predicted value).	Randomized, double-blind, parallel group, placebo-controlled trial.	Yearly rate of decline in the mean FEV_1 before the use of a study drug and short-acting bronchodilators in the morning (prebronchodilator) and after the use of a study drug (postbronchodilator) from day 30 (steady state) until completion of double-blind treatment, the rate of decline in the mean FVC and SVC, health-related quality of life, exacerbations of COPD and related hospitalizations, the rate of death from any cause and from lower respiratory conditions.	Tiotropium associated with improvements in lung function, quality of life, and exacerbations during a 4-year period but did not significantly reduce the rate of decline in FEV_1. Tiotropium reduced respiratory morbidity (including a decreased risk of respiratory failure) and reduced cardiac morbidity.

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in the SFC and tiotropium group, respectively; $p = 0.38$), but significantly higher in the tiotropium arm in patients with prior ICS use (126/319 *versus* 166/340; $p = 0.02$). Most strikingly, mortality was significantly lower in the SFC group during the study period, even though the trial was not powered to detect such a difference. There was >50% reduction in the risk of on-therapy all-cause death at any time during the study period for the SFC patients. Patients undergoing SFC treatment were also significantly less likely to withdraw from the trial than others.

The UPLIFT (Understanding the Potential Long-Term Impacts on Function with Tiotropium) trial [Tashkin *et al.* 2008], has been designed because a *post-hoc* analysis from Anzueto *et al.* [2005] suggested that tiotropium, a long-lasting antimuscarinic agent, can alter the rate of decline in FEV_1 over a 1-year period. This finding led to the hypothesis that tiotropium can alter the rate of decline in FEV_1 and may have long-term impacts on the course of COPD. The study included, 5993 COPD patients that were randomized 1:1 to receive 18 μg tiotropium once daily via HandiHaler or a matched placebo once daily *via* HandiHaler over 4 years, while allowing all patients to continue all prescribed respiratory medications other than inhaled anticholinergics. Therapy with tiotropium was associated with improvements in lung function, quality of life, and exacerbations during a 4-year period, but did not significantly reduce the rate of decline in FEV_1, which was the primary endpoint of the study. It is noteworthy to highlight that tiotropium produced a significant delay in time to first exacerbation by a median of 4.1 months ($p < 0.001$) *versus* control, a significant reduction in the number of exacerbations per patient year (14%; $p < 0.001$). In addition, it significantly reduced the risk of exacerbations leading to hospitalization (hazard ratio 0.86; $p < 0.002$) *versus* the control group. Another important finding was the fact that a statistically significant 16% decrease in the risk of death ($p = 0.016$) was observed in the tiotropium group while patients received treatment. Within the 4-year trial period, the effect on survival was sustained, even when deaths occurring after early discontinuation of study medication were included in the analysis ($p = 0.034$). Risk of mortality, assessed for the 30 days following the conclusion of the study, revealed an 11% reduction that was not statistically significance ($p = 0.086$).

Viewpoint

It is surprising that these large trials have all failed to reach their primary endpoints. A superficial analysis of their results could lead us to believe that the treatment of COPD is still largely insufficient. However, daily practice in real life shows that the proper use of drugs currently available to us allows good control of the disease, therefore we need to understand the real importance of these trials.

Apart from the fact that it is difficult to compare these studies directly as their design, patient population and duration were different, it is well known that long-term therapeutic trials are difficult to perform in patients with COPD. First, patients are not easy to recruit and maintain in long-term studies. Second, many patients with COPD suffer from concomitant diseases that often become dominant, influencing the outcomes of treatment. Third, adaptation of COPD treatment is usually in a step-up and not a step-down direction, such as used with some patients in many trials [Marchand, 2008]. Moreover, it is now well known that typical clinical study patients with COPD represent a very small fraction of the patient population being treated by clinicians in everyday practice, regardless of whether the doctors are pulmonary physicians or GPs [Herland *et al.* 2005].

In any case, what is really crucial is that we tend to consider and consequently treat COPD patients as a subject of a general population with the same characteristics because we consider COPD to be a homogeneous disease. However, COPD is a heterogeneous disease that has characteristics that occur with different phenotypes [Pistolesi *et al.* 2008]. Therefore, there is an urgent need to stratify studies based on a more detailed characterization of study subjects at baseline, thus approaching what Rennard and Vestbo [2008b] call 'many small COPDs' instead of a single large and heterogeneous COPD. It is likely that definition of these phenotypes will allow us to understand which patients will benefit from an ICS and which should only be treated with long-acting bronchodilators. Moreover, a revised view of COPD is required to define COPD subgroups, to develop relevant alternative biomarkers of disease progression, and to validate the targets already used for developing novel compounds [Rennard and Vestbo, 2008b].

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In the meantime, we must realize that, despite demonstrating benefits on important outcomes such as exacerbation frequency, symptoms, quality of life and other measures of health status, which are arguably more meaningful to individual patients than FEV_1 *per se*, these large trials have taught us disappointingly little about which patients with COPD are likely to benefit from intervention. As a result, there is little for the clinician to do but to treat all COPD patients similarly, despite their marked clinical heterogeneity [Cazzola and Matera, 2008]. Considering that, historically, the severity of COPD has been classified according to FEV_1, which may not correlate directly with symptoms, a symptomatic approach to therapy using clinical stages may be more useful [Cooper and Tashkin, 2005]. It seems appropriate that physicians should individualize treatment and try an additional type of drug if the patient symptomatically requires an alternative to be tried (and stop the additional drug if it does not seem to help) [Cazzola and Matera, 2008].

Obviously, all of the risks, costs and benefits of chronically inhaled medications for COPD should be weighed up before prescribing them. While the TORCH [Calverley *et al*. 2007] and INSPIRE [Wedzicha *et al*. 2008] studies tell us that patients under regular treatment with an ICS are at risk of pneumonia, the data from UPLIFT [Tashkin *et al*. 2008] indicate that tiotropium does not increase the risk of death, cardiovascular death, myocardial infarction and stroke. Furthermore, examination of all serious cardiac and all serious lower respiratory tract adverse events indicates that tiotropium is associated with a decreased risk of experiencing a serious adverse event in these organ classes. This information is reassuring because it comes from a large study that evaluated the impact of tiotropium for long time. This reassurance was absolutely necessary given that a recent meta-analysis has suggested that tiotropium increases the risk of myocardial infarction, stroke and cardiovascular death [Singh *et al*. 2008].

Conflict of interest statement

None declared.

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