European Respiratory Society study on chronic obstructive pulmonary disease (EUROSCOP): hypothesis and design


ABSTRACT: Chronic obstructive pulmonary disease (COPD) is a common disease in industrialised countries and responsible for a considerable morbidity and mortality. Cigarette smoking is the most important aetiological factor. The EUROSCOP trial aims at investigating the hypothesis that airway inflammation plays an important pathogenic role in the development of chronic obstructive pulmonary disease (COPD) 

In cigarette smokers with poorly reversible airflow obstruction, the effect over 3 yrs of an inhaled glucocorticosteroid, budesonide 400 μg b.i.d., on the decline of lung function, measured as postbronchodilator forced expiratory volume in one second (FEV1), will be compared with that of placebo. The trial has been designed to detect a difference in yearly decline of at least 30 m/year.

The study is a parallel group, randomised, double-blind, multicentre study. Patients will be recruited from 47 centres in 12 countries in Europe. It will start with a run-in consisting of two 3 month periods. During the first 3 months, the patients will be offered a smoking cessation programme. All patients who have not stopped smoking during this period will enter the second half of the run-in where compliance with the dosage regimen will be tested. After these two periods, patients will be randomised to receive either inhaled budesonide, 400 μg b.i.d., or placebo for a period of 3 yrs. 

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Chronic obstructive pulmonary disease (COPD) is a common disease in industrialised countries and responsible for a considerable morbidity and mortality [1]. Approximately 30% of smokers develop chronic cough and expectoration (“chronic bronchitis”) but only 15% of smokers develop chronic airflow obstruction or COPD [2, 3]. Cigarette smoking is the most important aetiological factor, but other factors such as environmental and occupational exposure, and genetic predisposition, are thought to play a role in the pathogenesis of COPD [4].

Cigarette smokers show an increased decline in lung function, and in approximately 15% this decline is of such a magnitude that the development of symptomatic disease can be expected, and is indeed observed when smoking is continued. However, even in subjects with an accelerated loss of lung function, medical help is very often only sought when an important degree of irreversible airflow obstruction has already been reached. These considerations clearly emphasize the need for early detection of the developing COPD and research on possible effects of therapeutic intervention.

The pathogenesis of COPD is unknown. Physiopathological studies demonstrate that the main localisation of the irreversible airflow obstruction is in the small airways [5]. The three major mechanisms for reduction in the calibre of the peripheral airways in COPD are: a chronic inflammatory process in the wall and the lumen of the peripheral airways, a loss of elastic recoil in the supporting alveolar structure and a destruction of the alveolar attachments to the outer wall of the small airways. Most recent data support the hypothesis that inflammation of the small airways is the primus mover in the pathogenesis of COPD [6]. Signs of inflammation in the peripheral airways include the presence of an increasing number of inflammatory cells (neutrophils, monocytes and lymphocytes), increased connective tissue deposition in the airway wall, epithelial metaplasia and ulceration in the epithelium.

Cessation of smoking has been shown to decrease the rate of decline of lung function in COPD and is, at this time, the only proven successful long-term therapeutic intervention in COPD [7].
The success rate of even the best smoking cessation programmes is limited and many smokers with COPD are unable to quit [8, 9]. Similarly, where occupational exposure plays a major role in the pathogenesis of the disease, various reasons may preclude a diminution of exposure. We therefore decided to test the hypothesis that treatment with an anti-inflammatory agent may slow the further loss of lung function in patients with COPD, despite continuous exposure to causally-related factors, in particular cigarette smoking.

The most potent available anti-inflammatory therapeutic agents are, without any doubt, glucocorticosteroids. Topically active inhaled glucocorticosteroids can be regarded as potent inhibitors of airway inflammation with a very low systemic availability, resulting in only a small risk for systemic side-effects. At the start of this trial, budesonide is the inhaled glucocorticosteroid with the best therapeutic ratio, and doses of up to 1 mg·day⁻¹ in adults are not associated with significant systemic side-effects [10].

Background to the study

Airway inflammation and COPD

Lesions of the small airways are thought to be the major determinants of the chronic airflow obstruction [5, 11]. Many of the pathological abnormalities of the small airways in COPD can be regarded as manifestations or sequelae of inflammation: airway narrowing, goblet cell hyperplasia, fibrosis, muscle hyperplasia, mucus plugging and loss of alveolar attachments [12].

Costo et al. [11] observed that the primary lesion in the small airways of patients with COPD was a progressive inflammatory reaction leading to fibrosis in the airway walls. The investigators scored the pathological abnormalities of the small airways in the lungs of patients undergoing thoracotomy. Their scoring system used eight variables, including the degree of occlusion of the airway lumen by mucus and cells, the presence or absence of mucosal ulcers, goblet cell hyperplasia, squamous cell metaplasia, the degree of inflammatory cell infiltration, the amount of connective tissue, the amount of muscle, and the amount of pigment in the airway wall. A significant relationship was found between the pathological changes in the airways and physiological parameters of peripheral airway obstruction, such as closing volume and the slope of the nitrogen wash-out curve. Physiological abnormalities were already measurable at a stage where the pathological abnormalities of the small airways were still potentially reversible. A few years earlier, Niewoehner et al. [6] had observed that the lungs of young smokers, who suddenly died outside the hospital, showed signs of respiratory bronchiolitis characterised by an increase in mura inflammatory cells and denuded epithelium in the membranous bronchioles. They hypothesised, that these small airway lesions may be responsible for the early physiological abnormalities observed in smokers and may be the precursors of more severe anatomical lesions.

Several pathological studies have confirmed the presence of inflammatory changes of the small airways in smokers, and their association with the characteristic physiological signs of developing COPD. Perry et al. [13] observed a significant relationship between preoperative physiological abnormalities characteristic of COPD, physiological abnormalities of the excised lungs, such as larger closing capacities, and pathological signs of inflammatory changes in the small airways, such as inflammatory cell infiltration, occlusion of airways by luminal cells and mucus, mural inflammation and increased airway muscle. In studies on patients undergoing lobectomy for a solitary pulmonary nodule, Wright and co-workers [14, 15] similarly observed, in lungs of smokers, inflammation in both respiratory and membranous bronchioles, goblet cell hyperplasia of the epithelium in membranous bronchioles, increases in wall fibrosis and pigmentation. In a subgroup of patients who smoked but still had a forced expiratory volume in one second (FEV₁) >80% predicted, an increase in the pathological signs of small airway inflammation was found in relationship to a decreasing FEV₁. Immunochemical studies of the peripheral airways of COPD patients, showed that these patients had more B-lymphocytes in the airway adventitia and that the number of submucosal polymorphonuclear leucocytes was related to the amount smoked [16].

The loss of elastic recoil is another determinant of airflow obstruction in COPD. In smokers, a significant decrease in the number of alveolar attachments and increase in both the distance between attachments and in the percentage of abnormal attachments, is correlated with the score for inflammation of the small airways and with the decrease in elastic recoil [17]. The presence of alveolar septal breaks must, indeed, be regarded as a precursor of the development of air-space enlargement in the lungs of smokers [18]. Therefore, small airways disease is thought to play a major causal role in the development of emphysema in smokers [19].

Investigations using bronchoalveolar lavage (BAL) show that in smokers with or without chronic airflow obstruction, there is an increase in the total number of cells recovered by lavage and a significant increase in the percentage of neutrophils [20]. Smokers with airflow obstruction have a significantly higher percentage of neutrophils in their BAL fluid than smokers without airflow obstruction. The macrophages in the BAL fluid of smokers with COPD release significantly more elastase than the macrophages of smokers with normal lung function [21].

The presence of an increased number of neutrophils and signs of activation of macrophages in the BAL fluid add further evidence to the hypothesis that inflammation of the airways and, as the pathology studies show more specifically of the small airways, plays an essential role in the pathogenesis of COPD.
Pathology studies suggest that the inflammatory changes in the small airways of smokers with mild to moderate COPD may still be, at least partially, reversible.

Glucocorticosteroids and progression of COPD

Both oral and inhaled glucocorticosteroids have been shown to be useful anti-inflammatory drugs in the treatment of asthma [22, 23]. In long-term studies, inhaled glucocorticosteroids have been shown to improve symptoms, need for extra bronchodilator medication, level of airflow obstruction, and severity of hyperresponsiveness. There are, as yet, however, no data on long-term, double-blind, placebo-controlled intervention studies with glucocorticosteroids in COPD [24]. Some controlled, short-term studies with oral glucocorticosteroids show variable results. They have tried to identify predictors of improvement in FEV\textsubscript{1} response. However, no consistent pattern has emerged from these studies: higher reversibility and sputum and blood eosinophilia have been found to be weak predictors of improvement by some authors but not by others.

Only two long-term intervention studies on oral glucocorticosteroids are available, both of a retrospective nature [25, 26]. These studies in patients with COPD, carefully excluding allergic individuals, show a favourable effect of glucocorticosteroids on the course of FEV\textsubscript{1} over 20 yrs of follow-up. A close association existed between the pattern of change in FEV\textsubscript{1} over time and the intake and dosage of prednisolone: below a dose of 10 mg\textperday\right^1 (e.g. 7.5 or 5 mg\textperday\right^1) FEV\textsubscript{1} declined continuously. When \geq 10 mg\textperday\right^1 was given, FEV\textsubscript{1} remained stable or even increased. Both studies also showed that a reduction below 10 mg\textperday\right^1, or cessation of prednisolone, resulted in an accelerated decline in FEV\textsubscript{1}. However, it took at least 6 months and up to 24 months before the effects on FEV\textsubscript{1} could be observed. This is in striking contrast to asthma, where glucocorticosteroids have an almost instantaneous effect. Since COPD is a slowly progressive disease, this delay in effect may simply reflect the difference in aetiology of the airflow obstruction (see above).

Short-term studies on inhaled glucocorticosteroids in COPD do not show a consistent improvement in baseline lung function, or in hyperresponsiveness [27–29]. One of these studies followed six men for one year in an open fashion and could not discern any effect on FEV\textsubscript{1} [29]. A few studies with short courses of inhaled glucocorticosteroids were unable to identify predictors of improvement in FEV\textsubscript{1}, possibly due to the relatively low numbers of patients involved [30–33].

There is only one abstract available on a 2 yr double-blind follow-up of non-allergic patients with COPD [34]. In this study, inhaled budesonide appeared to slow the fall in FEV\textsubscript{1}. Moreover, respiratory complaints decreased and the duration of exacerbations tended to be lower in the actively treated group. This study involved both smoking and ex-smoking patients. Although beneficial effects of inhaled glucocorticosteroids were observed in both groups, smoking still negatively influenced the decline in FEV\textsubscript{1}.

The above results suggest that it is worthwhile to look further into the effects of inhaled glucocorticosteroids in smoking patients with airflow obstruction, where decline in lung function is rapid. However, beneficial effects can only be expected after a reasonably long follow-up time.

Hypothesis

The EUROSCOP trial aims to investigate the hypothesis that airway inflammation plays an important pathogenic role in the development of chronic obstructive airway disease in smokers. The effect over 3 yrs of an inhaled glucocorticosteroid, budesonide, (given in a dose of 400 \(\mu\)g \textit{b.i.d.}) on the decline of FEV\textsubscript{1}, was compared with that of placebo. The trial has been designed to detect a difference in yearly decline of at least 30 ml\textperyear\right^1.

Objectives

The primary objective of the EUROSCOP study is to assess the efficacy of inhaled budesonide in reducing the accelerated annual decline of FEV\textsubscript{1} in smokers suffering from COPD with poor reversibility to beta\textsubscript{2}-agonists. The primary variable will be post-bronchodilator FEV\textsubscript{1}.

Patients and methods

Overall study design

The study is a parallel group, randomised, double-blind, multicentre study. Patients will be recruited from 47 centres in 12 European countries (see list at end of publication). It will start with a run-in consisting of two 3 month periods. During the first 3 months, the patients will be offered a smoking cessation programme. Patients who have not stopped smoking during this period will enter the second half of the run-in, where compliance with the dosage regimen will be assessed using an electronic device that records date and time of a correct inhalation. After these two periods, patients fulfilling all of the inclusion and none of the exclusion criteria will be randomised to receive either inhaled budesonide, 400 \(\mu\)g \textit{b.i.d.}, or placebo, for a period of 3 yrs (fig. 1).
ERS STUDY PROTOCOLS

Pulmicort Turbuhaler® 400 µg b.i.d.

Placebo b.i.d.

Fig. 1. — Schematic representation of the design of the EUROSCOP study.

The patients will visit the clinic four times a year at 3 months intervals during the randomised treatment period. A variation of ±14 days is allowed for each clinic visit; for example visit 3: 6 months ±14 days from visit 1; visit 4: 9 months ±14 days from visit 1. At these visits efficacy and safety will be assessed.

Patients

Number of Patients. About 1,000 patients will be randomised into the study. Taking into account the success of the smoking cessation programme, the compliance checking and number of withdrawals, approximately 2,500 patients should be enrolled at visit 1. Each centre will enrol about 50 patients.

Inclusion criteria. Out-patients of both sexes, aged 30-65 yrs can be included. They should be current cigarette smokers, having smoked for at least 10 yrs, or having a history of cigarette consumption equal to 5 pack-years, smoking at least 5 cigarettes·day⁻¹ at visit 1, and still smoking at visit 2 and 3. Their post-bronchodilator FEV₁ values must be 50-100% of the predicted normal values according to the European Community for Coal and Steel [35], at visit 1 whilst having a pre-bronchodilator FEV₁/vital capacity (VC) less than 70%. The reversibility of their airflow obstruction must be poor, defined as an increase in FEV₁ of <10% of the predicted normal value after 2 intakings of 0.5 mg terbutaline sulphate from a Turbuhaler, assessed at visit 1. The variability in FEV₁ values between visit 2 and visit 3 must not exceed 15% of predicted normal values, according to the formula:

\[
\frac{\text{FEV}_1(\text{visit 3}) - \text{FEV}_1(\text{visit 2})}{\text{FEV}_1} \times 100\%
\]

Exclusion criteria. Patients with a history of asthma, allergic rhinitis and/or allergic eczema are excluded from the study. Patients treated with oral glucocorticosteroids during a significant part (at least four weeks) of the last six months before entry into the study are equally excluded. Treatment with beta-blockers, long-acting inhaled beta₂-agonists (e.g. salmeterol or formoterol) is not allowed during the study.

Patients with a poor compliance, defined as less than 75% of total prescribed dosage regimen during the second three months of the run-in period, will not be randomised and treated.

Sample size determination. The primary end-point of the study is the slope of the post-bronchodilator FEV₁ values (ml·yr⁻¹). A difference in slopes between the placebo and budesonide groups of 30 ml·yr⁻¹ is thought to be clinically relevant. Literature on the standard deviation (σp) of the slope in COPD is scanty. Data extracted from ANTHONISEN et al. [36], and two recently completed Dutch studies [34, 37] led to an estimate for the σp of 100 ml·yr⁻¹ in patients with a complete follow-up of 3 yrs. A type I error (α, risk of a false positive result) of 0.05 and a type II error (β, risk of a false negative result) of 0.05 are chosen. The assumptions are made that the distribution of the slopes is approximately normal and that the standard deviation of the treatment groups is approximately equal. With the above estimates and choices made, the sample size follows:

\[N_{\text{min}} = 13.0 \times 2 \times \sigma_p^2 (\bar{\mu}_p - \bar{\mu}_l)^2 / 30^2 = 289\]

A withdrawal rate of 30-40% is deemed likely, but could possibly be higher. The required sample size is, therefore, rounded to 500 per treatment group.

This sample size will have an approximately 80% power (β=0.2) to find a difference in treatment response of 20 ml·yr⁻¹.

Drug handling and therapy

Study drugs. The study drug will be administered via a Turbuhaler, a multi-dose dry powder inhaler. The investigational drug is budesonide (Pulmicort), powder
for inhalation, 400 μg·dose⁻¹, 200 doses per Turbuhaler. The reference drug is Placebo Turbuhaler, powder for inhalation, containing lactose 200 μg·dose⁻¹, 200 doses.

**Randomisation.** A block randomisation generated by a computer programme will be used, and each centre will be randomised separately. Patient numbers will be allocated in a consecutive order at visit 3, after the run-in period and the smoking cessation. During the run-in periods patients will be identified by initials and by an enrolment number given at the first visit.

**Blinding Procedure.** All study inhalers, active drug and placebo will be of identical appearance throughout the study.

**Duration of treatment.** The run-in period is followed by a treatment period of 3 yrs (±3 months).

**Other therapy.** Inhaled glucocorticosteroids, other than study medication, are not allowed during the run-in and the study period. Oral or parenteral steroids are allowed only during exacerbations and to a maximal extent of 8 weeks·yr⁻¹. Chronic treatment with theophylline, mucolytics and oral beta₂-agonists is allowed, and should be maintained as constant as possible. Inhaled short-acting beta₂-agonists and anticholinergics are allowed as needed. Long-term treatment (i.e. more than 8 weeks·yr⁻¹) with inhaled long-acting beta₂-agonists, disodium cromoglycate or nedocromil sodium is not allowed. Similarly, treatment with beta-blockers is not allowed.

Other medication which is considered necessary for the patient's welfare may be given at the discretion of the investigator. The administration of all such drugs will be recorded in the appropriate section of the case record form.

**Spirometry: measurements and standardisation**

All centres participating in the EUROSCOP study have received the same type of spirometer, namely the dry rolling seal spirometer, Spirometrics SMI III, for use in this study. This spirometer automatically calculates and immediately interprets test tracings. It selects the best test results according to the recommendations of the American Thoracic Society, in addition to calculating the predicted and % predicted values. The spirometer used in the Euroscop study performs the corrections for saturated ambient temperature and pressure, saturated body temperature and pressure (ATPS-BTPS), automatically after input of barometric pressure and temperature. The spirometer has also in-built facilities for leak control, which are coupled to calibration. The reference values published by the European Community for Coal and Steel are used in the EUROSCOP trial [35].

Before the start of the study, all participating investigators and their lung function technicians were invited to a training session on spirometry and the use of the selected spirometer. Each centre will be visited regularly by a specially trained nurse during the study. This person will check that the spirometric measurements are performed accurately and to a high quality. These quality assurance visits will be documented and reported to the Steering Committee.

**Safety studies**

Long-term treatment with oral glucocorticosteroids is associated with risk of systemic side-effects. Inhaled glucocorticosteroids, such as budesonide, however, have, a high inhibitory effect on inflammation and a low risk of systemic effects due to the low systemic availability and low potency of major metabolites [10]. Possible adverse events that may occur with oral steroids are, for example, osteoporosis, hyperglycaemia, myopathy, posterior subcapsular cataracts, growth suppression, and Cushing's appearance. Adverse effects of inhaled steroids are few but may include adrenal suppression, hoarseness, oropharyngeal candidiasis and dysphonia.

Several clinical studies have shown that the adrenal suppression is very unlikely with therapeutic inhaled doses. Candidiasis and dysphonia are dose-related and seldom a problem, and candidiasis responds well to local therapy.

The Steering and Safety Committees have discussed the safety of long-term treatment with inhaled steroids in patients with COPD. Several experts on endocrinology, ophthalmology, pathophysiology and biochemistry have contributed to the discussions. The safety programme of the EUROSCOP study includes spontaneously reported adverse events and response to a standard questionnaire on diagnosis of conditions associated with steroid treatment at each visit, counting of skin bruises on both forearms at each visit, spine radiography before randomisation and at the end of the treatment period, bone density measurement, and blood tests for bone metabolism markers every six months to one year.

**Interim analysis**

The first interim analysis will take place after all patients have been followed for one year. Only patient withdrawals will be considered. The number of patients withdrawn on each treatment regimen will be compared. To allow for variable follow-up time, a log-rank test will be undertaken to compare times to withdrawal. A significant (p<0.001) difference will be a guideline for termination of a treatment regimen. When a significant difference is thus found, analysis of reasons for withdrawal will be undertaken.

The second interim analysis will be performed after two years. Two analyses will be undertaken, one with the primary end-point (slope of FEV₁) and one considering patient withdrawals. A two-sample t-test will be used to compare the slopes of
post-bronchodilator FEV₁ values (ml·yr⁻¹) between treatment groups with a significant \((p<0.01)\) difference being the guideline for termination.

When statistically significant differences between treatment groups can thus be claimed, this will be reported to the Safety Committee. Interim results will be reported to participating centres only if a decision to terminate has been made.

Organisation and administration

EUROSCOP is a collaboration between the European Respiratory Society (ERS) and ASTRA, sponsors of the project. The ERS is responsible for the organisational structure of the project and have appointed the members to the Steering Committee, Safety Committee and Scientific Committee (fig. 2). The Steering Committee is responsible for the scientific directions of the study at the operational level. It also recruited investigators and is responsible for the supervision of the progress of the study. The Scientific Committee is responsible for the scientific direction of the project and the final study protocol. The Safety Committee has a senior advisory function to the Steering Committee and periodically reviews and evaluates the study with regard to beneficial and adverse effects. The National Co-ordinators advise the local investigators and monitors on recruitment and questions from Ethics Committees. The study is performed in 47 Clinical Centres in 12 European countries.

Steering Committee


Scientific Committee

A.E. Tattersfield, Nottingham, UK; R. Dahl, Arhus C, Denmark; G.J. Huchon, Boulogne, France; B. Mossberg, Stockholm, Sweden; P. Paoletti, Pisa, Italy; R. Rodriguez-Roisin, Barcelona, Spain; J.Cl. Yernault, Brussels, Belgium.

Safety Committee

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Other personnel involved in the study


Advice and teaching on spirometry


External Advisors

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References

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