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Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE)

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Short title: The ECLIPSE study protocol

Abstract

COPD is a heterogeneous disease and not well understood. Forced expiratory volume in 1 second (FEV_1) is used for the diagnosis and staging of COPD but there is wide acceptance that it is a crude measure and insensitive to change over shorter periods of time. ECLIPSE is a 3 year longitudinal study with 4 specific aims: (i) to define clinically relevant COPD subtypes, (ii) to identify parameters that predict disease progression in these subtypes, (iii) to examine biomarkers that correlate with COPD subtypes and may predict disease progression, and (iv) to identify novel genetic factors and/or biomarkers that both correlate with clinically relevant COPD subtypes and predict disease progression. It is planned to recruit 2180 COPD subjects in GOLD categories II-IV, 343 smoking and 223 non-smoking control subjects. Study procedures will be performed at baseline, 3 months, 6 months, and then every 6 months. Assessments include pulmonary function measurements (spirometry, impulse oscillometry, and plethysmography), computed chest tomography, biomarkers (in blood, sputum, urine and exhaled breath condensate), health outcomes, body impedance, resting oxygen saturation and 6 minute walking distance. ECLIPSE is the largest study attempting to better describe the subtypes of COPD as well as defining predictive markers of COPD progression.

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Key words: Chronic obstructive lung disease, natural history, emphysema, lung function, biomarkers, genetics

Introduction

Chronic obstructive pulmonary disease (COPD) causes 2.75 million deaths annually, representing the fourth leading cause of death worldwide (1), and COPD is associated with substantial morbidity (2). COPD is a multicomponent disease comprising emphysema in the lung parenchyma, large central airway inflammation and mucociliary dysfunction, bronchiolitis and small airway structural changes (3). Together, these separate factors contribute to the chronic airflow limitation which characterises the condition (3,4). In addition, there is evidence that systemic inflammation and extrapulmonary effects are also common in COPD although the association between systemic inflammation and systemic manifestations of COPD is still not entirely clear.

Traditionally, both COPD diagnosis and evaluation of severity have been based on spirometry (5,6) and change in forced expiratory volume in 1 second (FEV_1) over time is still the most widely accepted measure of disease progression. However, FEV_1 has limitations as it measures only one aspect of the disease and is not predictive of disease progression, especially in early disease (7-9). In addition, patients with similar FEV_1 may have very different underlying pathology; e.g., predominantly air space disease (i.e. emphysema) or disease of the airways, as manifested by increased airway wall thickness (8). Additionally, patients with similar FEV_1 may also have different functional status. Thus, spirometric assessment alone is insufficient to characterise COPD and there is a clear need for a better understanding of the conditions that comprise COPD, which is a syndrome rather than a disease.

For the assessment of response to treatment of COPD there is also a need for measures of disease progression applicable and responsive to interventional research. While FEV_1 decline has to date been regarded as the gold standard, different measures are likely to provide a more specific assessment of disease activity and progression within clinical

subtypes of COPD. Also, a substantial length of observation time is required for using FEV_1 decline as a measure of progression and biomarkers that over a shorter time could evaluate progression would be useful.

The ECLIPSE study (Clinicaltrials.gov identifier NCT00292552; GSK Study Code SCO104960) is a 3-year longitudinal study with the overall objective of identifying the parameters that predict disease progression in individuals with different COPD subtypes as well as biomarkers that may serve as surrogate endpoints. This manuscript describes the purpose and design of the study.

Methods

Study objective

The ECLIPSE study has the following specific aims:

1. To use questionnaires, spirometry, exercise testing and computed tomography (CT) to define clinically relevant COPD subtypes in individuals with GOLD stage II-IV COPD.
2. To identify and define the parameters that predict disease progression over 3 years in clinically relevant COPD subtypes in individuals with GOLD stage II-IV COPD. For the purposes of the study disease progression will be defined by changes in lung function variables, symptoms, exacerbation frequency, exercise capacity and airway/lung parenchymal changes on chest CT scans.
3. To measure known biomarkers in blood, urine, sputum and breath condensate in order to identify those that correlate with clinically relevant COPD subtypes in individuals with GOLD stage II-IV COPD and which may serve as markers of disease progression.

4. To use genetic analysis, proteomics, RNA transcriptomics and metabolomics to identify novel genetic factors and/or biomarkers that correlate with clinically relevant COPD subtypes in individuals with COPD and with one or more of the markers of disease progression.

Study design

ECLIPSE is an ongoing 3-year, non-interventional, longitudinal prospective study being conducted at 46 centres in 12 countries. Following a baseline visit subjects will be followed-up at seven visits in total: 3 months, 6 months and then every 6 months thereafter for 3 years. In addition to the study visits, COPD patients will be telephoned each month between clinic visits to assess exacerbation rates. All subjects will continue to receive their normal prescribed medications throughout the study; no medications are prohibited during the study. The study is being conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines and has been approved by relevant ethics and review boards at the participating centres.

Subject participation

A planned total of 2180 COPD patients aged 40–75 years, with baseline post-bronchodilator FEV_1<80% predicted, baseline post-bronchodilator $FEV_1/FVC \leq 0.7$, and a smoking history of ≥10 pack years will be enrolled. In addition, 566 control subjects (post-bronchodilator FEV_1>85% predicted and $FEV_1/FVC > 0.7$), aged 40–75 years will be recruited, forming two groups: controls with a smoking history ≥10 pack years (n=343) and 223 non-smoking controls with <1 pack year. Inclusion criteria for COPD patients and control subjects are shown in Table 1. Exclusion criteria were related to diagnosis (known respiratory disorders other than COPD and severe α_1-antitrypsin deficiency), prior medical history (known history of significant inflammatory disease other than COPD, a COPD exacerbation within 4 weeks of enrolment, having undergone lung surgery, recent

diagnosis of cancer, having received a blood transfusion in the 4 weeks prior to study start, inability to walk, taking part in a blinded drug study, therapy with oral corticosteroids at inclusion, and participation in studies with radiation exposure. In addition, the usual criteria of serious, uncontrolled disease likely to interfere with the study or impact on subject safety and substance abuse were applied.

Outcome measurements

Endpoints being measured in ECLIPSE include lung physiology, imaging, biomarkers, health outcomes and genetics. The endpoints are listed in table 2; they are not listed in order of importance.

Measures of lung physiology and imaging are central parameters. All subjects will have spirometry and impulse oscillometry performed at all study visits. Body plethysmography measurements will be made annually at selected sites with recording of static lung volumes, airway resistance and specific conductance. Biomarkers in blood will be assessed at all sites whereas sputum, urine and exhaled breath condensate will be collected at selected sites. At baseline, after 1 year and after 3 years all subjects will have a low-dose volumetric (120 kVp, 40 mAs, 1 or 1.25 mm slice thickness) CT scan at full inspiration. The radiation dose is estimated to be 1.67 mSev per CT study or 5 mSev for the entire ECLIPSE protocol. All scans are sent for evaluation at the central imaging unit at University of British Columbia in Vancouver.

Study organisation

The study is being guided by a Steering Committee consisting of 5 academic physicians and representatives of the study sponsor, GlaxoSmithKline. A scientific committee of 6

academic investigators reports to the steering committee on specific scientific issues and proposals for sub-studies.

Discussion

COPD is characterised by abnormal spirometry, with a focus on FEV_1. Since small airways disease is an important component of COPD, and FEV_1 is not very sensitive to changes in small airway calibre, other measures may more accurately reflect small airway function. In addition, FEV_1 is insensitive to the severity of emphysema in COPD and patients with similar FEV_1 may have very different underlying pathology. As an assessment of severity, FEV_1 correlates poorly with clinical parameters (e.g. dyspnoea, quality of life, costs of care). For following COPD over time, studies using decline in FEV_1 to assess COPD progression typically require a minimum of 3 years and the costs and efforts associated with studies of 3 years duration or longer limit the number of novel drugs that can be considered for disease modification. Finally, although FEV_1 as well as other measures of lung function can be used for prognostic purposes, the association between mortality and FEV_1 is considerably stronger when other measures are added to the predictive equation (10). Clearly, more sensitive measures of assessing COPD severity and disease progression are needed. Such measures should ideally reflect several components; e.g., inflammation, structural changes, disease activity, impact on patients' lives, and prognosis.

Airway inflammation is a key component of the pathogenesis of COPD (5,6). The inflammation can be characterised by different cell differential profiles, which may reflect different inflammatory subgroups (11,12), as well as increased levels of various inflammatory mediators (13,14). Airway inflammation can to some extent be studied non-invasively using induced sputum and exhaled breath condensate (EBC), and both measures

are applied to subsets of the ECLIPSE population. Systemic inflammation in COPD is increasingly recognised as an important feature of COPD (15). So far, CRP has been reviewed most extensively; however, a number of other markers may be of importance and profiling of systemic inflammation is important in ECLIPSE.

CT-scanning is a crucial element in ECLIPSE to determine different pathogenic phenotypes. We will conduct 3 low-dose volumetric CT-scans and quantitative analysis using CT lung density measurements to evaluate both degree and distribution of emphysema and airway wall dimensions as a tool for splitting COPD in subgroups based on structural changes and to evaluate disease progression (16). This area is clearly not fully developed yet but previous data suggest that risk factors for COPD may differ depending on identification of emphysema / airway remodelling on CT.

Exacerbations are important events influencing disease severity, health related quality of life, disease progression and mortality (17), and characterisation of frequency, type and duration of exacerbations could be of significant importance. In ECLIPSE, all subjects are contacted monthly by phone with a structured interview scheme in order to capture exacerbations. Other more detailed tools such as diary cards may have been more accurate for this characterisation but were considered unfeasible in a population of this size from several different countries.

Various other health outcome measures have been correlated with COPD progression. Breathlessness, which in ECLIPSE is measured using a modified MRC dyspnoea scale, is an independent predictor of mortality (18). The same is the case for SGRQ scores (19) and exercise capacity (20). In general, it is unlikely that any single outcome measure will

accurately predict clinical progression in all COPD patients; ECLIPSE aims to examine whether the BODE index (10) or other prognostic indices may have value across different COPD subtypes.

Comorbidities in COPD are of importance as they are frequent and affect prognosis as well as costs of COPD (21). In ECLIPSE we have chosen not to exclude subjects with cardiovascular comorbidities unless they are of a severity that makes it unlikely that patients can complete a 3-year study. We have, however, chosen to exclude diseases with significant systemic inflammation such as rheumatoid arthritis and inflammatory bowel disease. We are aware that this could potentially introduce a bias or at least reduce the generalisability of our findings somewhat but we would rather run that risk than contaminate the population with non-COPD related systemic inflammation.

The major dilemma of a study like ECLIPSE which is aimed at finding surrogate markers superior to FEV_1 is the fact that the gold standard for both diagnosis and assessment of rate of progression is currently FEV_1. The challenge of this study is therefore to utilise the varied information gathered to describe models of COPD rooted in our classic definition of COPD but with much more detail and an ability to capture the dynamics of the different processes that result in the clinical subgroups that eventually make up the syndrome we today call COPD. It is recognised that putative surrogate endpoints identified from ECLIPSE would need to be further tested in subsequent studies.

In conclusion, ECLIPSE is the first study in a large number of subjects with the primary objective of describing the subtypes of COPD, defining predictive or surrogate markers of disease progression and possibly identifying novel targets for therapeutic intervention.

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Table 1. Inclusion criteria for ECLIPSE

COPD Subjects

1. Male or female subjects, aged 40-75 years inclusive
2. A baseline (post-bronchodilator) FEV_1 <80% of predicted normal and a baseline (post-bronchodilator) FEV_1/FVC ratio ≤ 0.7
3. Current or ex-smokers with a smoking history of at least 10 pack-years (number of pack years = (number of cigarettes per day / 20) x number of years smoked e.g., 20 cigarettes per day for 10 years, or 10 cigarettes per day for 20 years)
4. A signed and dated written informed consent is obtained prior to participation.
5. Able to comply with the requirements of the protocol and be available for study visits over 3 years

Control Subjects – Smokers

1. Male or female subjects, aged 40-75 years inclusive, who are free from significant disease as determined by history, physical examination and screening investigations
2. Baseline (post-bronchodilator) FEV_1 >85% of predicted normal. FEV_1/FVC ratio >0.7
3. Current or ex-smokers with a smoking history of at least 10 pack-years (number of pack years = (number of cigarettes per day / 20) x number of years smoked e.g., 20 cigarettes per day for 10 years, or 10 cigarettes per day for 20 years)
4. A signed and dated written informed consent is obtained prior to participation
5. Able to comply with the requirements of the protocol and be available for study visits over 3 years

Control Subjects – Non-smokers

1. Male or female subjects, aged 40-75 years inclusive, who are free from significant disease as determined by history, physical examination and screening investigations
2. Baseline (post-bronchodilator) FEV_1 >85% of predicted normal. FEV_1/FVC ratio >0.7
3. Non-smokers with a smoking history of < 1 pack-year (number of pack years = (number of cigarettes per day / 20) x number of years smoked)
4. A signed and dated written informed consent is obtained prior to participation
5. Able to comply with the requirements of the protocol and be available for study visits over 3 years

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Table 2. Outcomes measured in ECLIPSE

Assessment	Description	Time of assessment*
Pulmonary function		
Lung function: post-bronchodilator FEV_1, rate of decline in FEV_1, FVC, FEV_1/FVC ratio, FEV_6, SVC, reversibility		Each visit
Pulmonary plethysmography: RV, TLC, FRC, airway resistance, specific conductance[†]		Annually
Impulse oscillometry: frequency-dependent resistance and reactance parameters	To measure peripheral airways function during tidal breathing	Each visit
Exhaled carbon monoxide	To confirm smoking status	Each visit
Whole body impedance/fat-free mass		
Body composition	Estimated using single frequency (50kHz) bio-electrical impedance analysis	Annually
Fat-free mass	Calculated from $height^2$/impedance, age,	Annually

	gender and body weight	
Computed tomography (CT)		
Chest CT scan – COPD subjects and smoking controls Chest CT scan – non-smoking controls	Will measure airway dimensions and quantify emphysema ; will be used to stratify patients during data analysis	Years 1 & 3 Baseline only
Exercise capacity		
6 minute walk test (6-MWT) – COPD patients only	Supervised standardised 6-MWT	Annually
Oxygen saturation		
Resting oxygen saturation	Measured after a 10-minute rest	Each visit
Biomarkers	To evaluate association with disease subtypes and their relationship with disease progression	
Blood samples: CRP, TNF-α, IL-6, Clara Cell Protein, IL-8, surfactant D proteins or mRNA	Measured using open platform technologies (transcriptomics, proteomics) or using specific validated assays (ELISA, multiplex, quantitative reverse transcriptase PCR)	Each visit
Induced sputum[†]: inflammatory	Total and differential cell	Annually

cell content, soluble markers (e.g. myeloperoxidase) and mRNA expression in cells	count, supernatant proteomics and cell extract transcriptomics	
Exhaled breath condensate†	Collected by the cooling and freezing of spontaneously exhaled air	Year 3
Blood and urine metabolomics†	Taken after 3-hour fast following completion of food intake diary	Each visit
Health outcomes		
Exacerbation assessment	Details of doctor or hospital visits recorded; use of oral corticosteroids or antibiotics recorded	Each visit plus monthly phone calls
ATS Respiratory Questionnaire	Standardised ATS epidemiology questionnaire	Baseline only
Depression Questionnaire	Centre of Epidemiological Studies Depression Scale (CES-D)	Year 3
Fatigue Questionnaire	FACIT Fatigue Scale	Year 3
Health status and MRC dyspnoea assessment	SGRQ-C; modified MRC dyspnoea scale; BODE index; Prognostic index	Annually
Blood samples for genetic markers		
DNA	To identify and/or confirm	Ongoing

	genes believed to be associated with COPD-related phenotypes and COPD subtypes

Abbreviations: ATS = American Thoracic Society; BODE = body-mass index (B), airflow obstruction (O), dyspnoea (D) and exercise capacity (E); CRP = C-reactive protein; FACIT = Functional Assessment of Chronic Illness Therapy; FEV_6 = forced expiratory volume in 6 seconds; FRC = functional residual capacity; IL = interleukin; MRC = Medical Research Council; RV = residual volume; SGRQ-C = St Georges Respiratory Questionnaire (for COPD); SVC = slow vital capacity; TLC = total lung capacity; TNF-α = tumour necrosis factor-α

*In addition to baseline

†At selected sites involving 500–510 individuals