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The Study to Understand Mortality and Morbidity in COPD (SUMMIT) Study protocol.

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Abstract (177 words)

Chronic obstructive pulmonary disease (COPD) often coexists with other chronic diseases and comorbidities that can markedly influence patients' health status and prognosis. This is particularly true for cardiovascular disease (CVD). However, there have been no trials assessing the effect of COPD medications on CVD in patients with both diseases.

The "Study to Understand Mortality and MorbidITy in COPD" (SUMMIT) aims at determining the impact of Fluticasone Furoate / Vilanterol combination (FF/VI), and the individual components on the survival of patients with moderate COPD and either a history of CVD or at increased risk for CVD.

SUMMIT is a multi-center, randomised, double-blind, parallel-group, placebo-controlled trial of 16,000 patients with moderate COPD randomly assigned to once daily treatment with FF/VI (100/25 mcg), Fluticasone Furoate (100 mcg), Vilanterol (25 mcg) or matched placebo; mortality is the primary endpoint. The study is an event-driven trial powered on the comparison of FF/VI vs. placebo. Secondary endpoints are decline in forced expiratory volume in 1 second (FEV_1) and effect on a composite cardiovascular endpoint. This manuscript describes the design of the SUMMIT study.

Keywords: COPD; CVD; protocol; study design; mortality; survival; Fluticasone Furoate; Vilanterol; combination therapy.

Introduction

The morbidity and mortality of chronic obstructive pulmonary disease (COPD) continues to rise [1]. It is increasingly recognized that COPD often coexists with other chronic diseases and that comorbidities can contribute to patients' health status and prognosis [2, 3]. Some of the changes seen in patients with COPD have been termed extra-pulmonary manifestations of COPD and typically include features that are believed to be linked to progression of COPD such as skeletal muscle dysfunction [4], lean mass depletion [5], and osteoporosis and osteopenia [6].

Other comorbidities are not so obviously linked to disease progression and these include cardiovascular disease (CVD). Several prospective studies have reported an association between impaired pulmonary function and cardiovascular morbidity and mortality [7-10] even after adjusting for accepted CVD risk factors. Epidemiological data suggest that patients with COPD are at a greater risk of CVD compared with age and gender-matched controls without COPD [11]. Furthermore, more patients with mild-moderate COPD die from lung cancer and cardiovascular diseases such as coronary artery disease and stroke than from the respiratory effects of COPD [12-14]. Systemic inflammation has been proposed as having a potential role in explaining the association between COPD and increased risk of CVD [15]. Other factors have also been implicated, including autonomic imbalance, vascular endothelial dysfunction, lower arterial compliance and arrhythmias. It is, however, also possible that the decreased physical activity associated with even mild COPD [16] may increase the risk of CVD as well as other comorbidities.

The current Global Initiative for Obstructive Lung Diseases (GOLD) strategy document has highlighted the need to assess and treat comorbidities in COPD [1]. For most CVD, the advice is to treat the comorbidity as if the patient did not have COPD and to treat COPD as in patients

without CVD. However, the evidence base for treating COPD patients with comorbidities is weak and most advice comes from expert statements or from secondary analyses of large studies. An example of the latter is the secondary analysis of the TOwards a Revolution in COPD Health study (TORCH), that focused on the safety of COPD medications in patients with concomitant CVD entered into this large 3-year study [17]. In addition to providing confidence in the safety of treating these patients with salmeterol alone or in combination with fluticasone propionate, the study also indicated that treatment with combined salmeterol and fluticasone propionate could have beneficial effects on risk of cardiovascular adverse events. Similarly, combination treatment seemed to have a similar effect on respiratory and cardiovascular mortality in the primary TORCH report [14]. It therefore seems reasonable to hypothesise that combination treatment may have a beneficial effect on survival in patients with COPD and concomitant CVD.

The Study to Understand Mortality and Morbidity in COPD (SUMMIT) is designed to prospectively compare the efficacy of Fluticasone Furoate and Vilanterol combination (100/25 mcg), or singly as Fluticasone Furoate (100 mcg) or Vilanterol (25 mcg) against matched placebo once daily via the Novel Dry Powder Inhaler on survival in subjects with moderate COPD and a history of, or at increased risk for, CVD. The study will test the hypothesis that treatment with combined inhaled corticosteroids and long-acting beta-agonists will reduce mortality when compared with placebo. As most patients with severe or very severe airflow limitation will require treatment with long-acting bronchodilators and possibly inhaled corticosteroids, and because comorbidities seem independent of severity of airflow limitation [2-5], the study will include patients with moderate airflow limitation only. This manuscript describes the protocol design and the approaches taken in this study that we anticipate will have important implications for the future treatment of patients with COPD.

Methods

SUMMIT study design

This is an international, multi-centre, placebo-controlled, double-blind, randomised, parallel-group trial, with patients expected to contribute 15-44 months of study time. The study involves a 4-10 day run-in period, a treatment phase and a one-week follow-up phase. The length of the treatment phase will depend on the mortality rate in the study; the study will last until 1000 deaths have been recorded. All prior use of inhaled corticosteroids (ICS) and inhaled long-acting bronchodilators will be discontinued at entry to the run-in period. The population sought are those patients with COPD that the practitioner believes can be adequately managed without these medications. Patients will be treated on an out-patient basis and clinic visits will occur at screening, randomisation, 4 weeks, and then every 12 weeks until the study has reached the required number of events.

Interventions

A total of 16,000 patients with moderate COPD and a history of, or at increased risk for, CVD will be randomised from approximately 1,100 sites to one of the following four treatment groups: placebo, a once-daily ICS Fluticasone Furoate (FF, 100 mcg), a once daily inhaled $beta_2$-agonist Vilanterol (VI, 25 mcg) or combined Fluticasone Furoate and Vilanterol (FF/VI, 100/25 mcg), administered once daily via the Novel Dry Powder Inhaler™. A separate randomisation schedule will be produced for each country. Patients who withdraw prematurely from study treatment will still be followed-up through regular contact until study termination to determine survival status. The study is listed on ClinicalTrials.Gov (NCT01313676).

Organizational Committees

The study is being guided by a Steering Committee consisting of external clinical experts and representatives of GlaxoSmithKline. An independent Safety and Efficacy Data Monitoring Committee is overseeing the ethical and safety interests of the patients by periodically reviewing results of interim analyses and cumulative data on serious adverse events. A Clinical Endpoint Committee is independently reviewing and categorizing the cause of death as well as events that are part of the cardiovascular composite end-point for each patient where an event has been recorded. The membership of the committees is provided at the end of this article.

Patient Participation

Recruitment commenced in March 2011 and is expected to conclude in late 2013. Patients are 40–80 years old with a smoking history of ≥10 pack-years, a clinical diagnosis of COPD with $FEV_1/FVC < 0.70$ and moderate airflow limitation, defined as a post-albuterol/salbutamol FEV_1 ≥50 and ≤70% of predicted normal values calculated using NHANES III reference equations [18, 19]). In addition, patients are required to have a history of CVD or to be at increased risk for CVD. The inclusion and most important exclusion criteria are summarised in Table 1.

Patients who have an exacerbation of COPD during the run-in period that requires systemic corticosteroid therapy or hospitalization will not be eligible for randomization. Patients are allowed to take COPD medication except for ICS, long-acting bronchodilators and long-term oral corticosteroids. Tiotropium use will not be permitted at baseline. However, if during the double-blind treatment phase, a subject experiences a severe COPD exacerbation (i.e., requiring hospitalization) and requires additional treatment or experiences multiple moderate exacerbations, tiotropium may be added. Tiotropium can also be added by the investigator

following a discussion with the study medical monitor if the investigator believes the addition is warranted to improve the management of the subject's disease. All patients will be offered salbutamol as relief medication.

The study is conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines. All patients will have given written informed consent before participating in the study. Ethics and Review Boards of all participating institutions have approved this protocol.

Efficacy and health outcome assessments

The primary endpoint measure will be all-cause mortality. Secondary endpoints and other objectives are given in Table 2. An important secondary end-point is the cardiovascular composite endpoint comprising of on-treatment cardiovascular death, myocardial infarction, stroke, unstable angina and transient ischemic attack (TIA); more details are provided in the e-supplement.

Survival status

Survival status of each subject will be recorded at every visit. For any subject who prematurely withdraws, survival status will be captured at 3-monthly intervals by means of telephone calls or other forms of contact. Accurate assignment of cause of death is essential. The investigator will assign a cause of death based on contact with the attending physician (where possible), details given on the death certificate, autopsy findings (if any) and any other available clinical evidence. Categorization of cause of death will also be done centrally by a Clinical Endpoint Committee (CEC) who will review study data and any additional information available (e.g., details given on the death certificate, autopsy findings, and any other available clinical evidence). The categorization of cause of death assigned by the CEC will be the primary basis

for all analyses for specific cause of death. The CEC will build on decision rules developed in the TORCH study [20].

Clinical safety assessments

Each adverse event or concurrent illness during the study will be documented in the case report form (CRF). For the purpose of this study, a moderate COPD exacerbation is defined as an exacerbation treated with antibiotics and/or systemic corticosteroids whereas a severe COPD exacerbation required hospitalization. In this study, pneumonia is defined as new auscultatory findings compatible with parenchymal lung infection and/or radiographic evidence of parenchymal/air space disease. A confirmed diagnosis of pneumonia must be recorded as an adverse event. Patients with worsening COPD status or progressive CVD while on study treatment can receive other medications, or be withdrawn if in the investigator's opinion the patient's deterioration prevents ongoing participation. The reason for withdrawal will be recorded and patients will be followed up until study termination.

One formal interim analysis of the time to death from any cause is planned in addition to the final analysis. It is intended that this analysis will be performed when approximately 50% of the total deaths have been observed. The analysis method for this will be the same as to be used in the final analysis i.e. Cox proportional hazards model.

Statistical analysis

This event driven study is designed to have 90% power to detect a 30% reduction in the risk of all-cause mortality (hazard ratio=0.70) on FF/VI compared with placebo at the two-sided 1% significance level. In order to detect this reduction, 478 events (on FF/VI and placebo combined) would be required.

The effects of the components (FF and VI) are expected to be lower than for FF/VI. The study is not powered for comparisons of the components to placebo or for the combination to components. If the true mortality rates for the components are intermediate between FF/VI and placebo, then it would be expected that by the time there are 478 deaths between the FF/VI and placebo arms there should be a roughly similar number on the component arms combined, which would give a total of 956 on 4 arms. However, since the study is blinded and it will be unknown exactly how many deaths will have occurred on the FF/VI and placebo arms when it stops, a balance must be struck between ensuring it runs long enough to accrue 478 deaths on those arms versus continuing the study for longer than necessary. Therefore a total number of 1000 deaths (between 4 arms) will be used to trigger stopping of the study for the final analysis.

The primary efficacy endpoint of time to all-cause mortality will be analysed using a Cox proportional hazards regression model allowing for important pre-defined covariates that may include, but not be limited to, baseline FEV_1, BMI, geographical region and smoking status.

Discussion

COPD often coexists with other conditions, in particular CVD. Importantly, the presence of one disease significantly affects the prognosis of the other. In this context, there is a need for evidence-based outcomes to support the efficacy of therapeutic modalities for the treatment of patients with COPD with concomitant CVD or its risk factors. As such, the SUMMIT trial aims to evaluate the impact of inhaled COPD therapy in patients with moderate COPD with, or at high risk for, CVD on all-cause mortality.

COPD and CVD may coexist for a number of reasons. A list of the most prominent mechanisms suggested is shown in Table 3. Smoking is clearly an important shared risk factor

and physical inactivity and deconditioning caused by COPD can clearly contribute to the risk of CVD. However, there may also be pathobiological links between the two diseases as a result of systemic inflammation that is common to both diseases. Inflammation in the small airways has been established as an initial event in the pathogenesis of COPD [21, 22] and its magnitude relates to the degree of airflow obstruction [22]. Recent studies suggest that the systemic inflammation seen in some patients with COPD may promote the development of atherosclerosis [23], the underlying cause of most ischemic heart disease. In addition, systemic inflammation related to COPD (i.e., endothelial dysfunction) can produce structural changes (e.g. elastin fragmentation and degeneration, increased collagen) and functional changes (e.g., reduced nitric oxide) in the wall of the aorta and medium-sized arteries resulting in decreased elasticity and increased stiffness [24]. Increased arterial stiffness is an independent predictor of all-cause and cardiovascular morbidity and mortality in hypertensive patients [25-27], as well as a predictor of cardiovascular events in general populations [28, 29].

The extent to which these types of data apply to patients with COPD is of increasing interest. Zureik et al demonstrated that carotid-femoral pulse wave velocity (PWV) was negatively associated with FEV_1 [30]. Moreover, Sabit et al compared PWV in COPD patients with healthy smokers and ex-smokers who were free of cardiovascular disease and confirmed its negative relation to FEV_1 [31]. In addition, by multiple regression analysis, the circulating cytokine interleukin-6 (IL-6) was a strong predictor of PWV in this study. The large ECLIPSE cohort study of patients with COPD showed that the presence of serum markers of inflammation increased the capacity to predict mortality compared with validated clinical predictors [32]. Increased PWV and elevated serum C-reactive protein (CRP) have also been demonstrated in patients with COPD compared with controls matched for age and smoking history [33]. These

latter findings may be important as CRP is related to, and is a predictor of, cardiovascular risk [34]. Finally, in a cross-sectional study McAllister et al demonstrated that emphysema severity, as assessed by quantitative high-resolution computerized tomography, is independently associated with arterial stiffness [35]. These observations raise the potential of a possible link between the pulmonary and systemic inflammation observed in COPD, with impaired larger artery compliance as an important factor underlying the increased cardiovascular morbidity and mortality that has been observed in intervention studies [10, 14]. Carotid-femoral pulse wave velocity will be measured in a subset of patients in the SUMMIT trial at sites in the United States and the United Kingdom.

Inhaled corticosteroids (ICS) have not been shown to reduce mortality in COPD. However, ICS do improve lung function and reduce exacerbations, both alone and in combination with a long-acting beta-agonist [36, 37]. It is possible that the reduction in exacerbations in itself could result in a reduced risk of CVD events. McAllister et al recently showed that patients admitted with a COPD exacerbation are likely to experience ischaemic events during this episode [38]. In the EUROSCOP study, long-term treatment with budesonide reduced ischaemic cardiac events in patients with mild COPD [39] without significantly affecting the risk of severe exacerbations. It is therefore likely that ICS in themselves may have benefits in patients with comorbid CVD.

The SUMMIT trial contains a placebo arm and this requires some consideration. All patients will be provided with a short-acting bronchodilator for relief and this is accordance with current COPD management strategies [1]. In addition, although potentially important, none of the tested medication classes in SUMMIT have been shown to provide long-term benefits to patients with COPD and this is an important gap in the evidence base. The SUMMIT trial is a long-term study in COPD and it may be prone to some of the biases observed in long-term trials in COPD

resulting particularly from withdrawal [40]. However, using an event-driven design may reduce the risk of dilution bias. The study will use the same strict trial review as in the TORCH study including intensive follow-up and adjudication of deaths and CVD events. The SUMMIT study will be one of the largest multi-centre, long-term COPD studies, and the first to investigate the effect of inhaled medications in patients with COPD and concomitant CVD. The data gathered may shed new light on the natural history of both these disorders.

Members of the Steering Committee

Robert Brook (USA), Peter Calverley (UK), Bartolome Celli (USA), Fernando Martinez (USA), David Newby (UK), Jørgen Vestbo (co-chair, Denmark),
Julie Anderson (GlaxoSmithKline, UK), Courtney Crim, GlaxoSmithKline, USA) Brett Haumann (co-chair, GlaxoSmithKline, UK), Julie Yates (GlaxoSmithKline, USA).

Members of the Safety and Efficacy Data Monitoring Committee

Peter Lange (chair, Denmark), Richard Kay (UK), Mark Dransfield (USA), Sanjay Rajagopalan (USA).

Members of the Endpoint Committee

Robert Wise (chair, USA), Dennis Niewoehner (USA), Camilo Gomez (USA), Sheldon Madger (Canada), Martin Denvir (UK).

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Table 1: Inclusion and exclusion criteria for the SUMMIT Study

Key Inclusion criteria:

- Male or female aged 40–80 years old
- Current or ex-smokers with a smoking history of ≥10 pack years
- An established history of COPD with an FEV_1/FVC ratio <0.70 and an FEV_1 ≥50 and ≤70% of predicted normal

A history of CVD or to be at increased risk for CVD:

- For patients ≥40 years of age this is defined as any one of the following: Established coronary artery disease (CAD), established peripheral vascular disease (PVD), previous stroke, previous MI or diabetes mellitus with target organ disease.
- For patients ≥60 years of age, any 1 of the above or 2 of the following will suffice: Being treated for hypercholesterolemia, being treated for hypertension, being treated for diabetes mellitus or being treated for peripheral vascular disease.

Key Exclusion Criteria:

- Current diagnosis of asthma or respiratory disorders other than COPD
- Chest x-ray indicating diagnosis other than COPD
- Had a lung-volume reduction surgery and/or a lung transplant
- Requirement for long-term oxygen therapy at start of study (more than 12-hours per day)
- Receiving long-term oral corticosteroid therapy
- Current severe heart failure (New York Heart Association class IV). Subjects will also be excluded if they have a known ejection fraction of <30% or if they have an implantable cardioverter defibrillator (ICD).

- Any life-threatening condition with life expectancy <3 years, other than vascular disease or COPD, that might prevent the subject from completing the study.
- End-stage chronic renal disease

SUMMIT: The Study to Understand Mortality and Morbidity in COPD; COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity

Table 2: Secondary endpoints and other objectives in the SUMMIT Study

Secondary endpoints:

- To evaluate the effect of FF/VI compared with placebo on the rate of decline in FEV_1
- To evaluate the effect of FF/VI compared with placebo on a cardiovascular composite endpoint comprised of on-treatment CV death, myocardial infarction, stroke, unstable angina and TIA.

Other objectives:

- To evaluate the following treatment comparisons on all primary, secondary, other and exploratory endpoints: FF/VI compared with FF, FF/VI compared with VI, FF compared with placebo, and VI compared with placebo
- To evaluate the effect of FF/VI compared with placebo on the rate of moderate/severe COPD exacerbations
- To evaluate the effect of FF/VI compared with placebo on COPD-related mortality
- To evaluate the effect of FF/VI compared with placebo on arterial stiffness in a subset of subjects
- To evaluate the effect of FF/VI compared with placebo on health-related quality of life measured with the SGRQ-C in a subset of subjects
- To evaluate quality-adjusted life years (QALYs) by treatment group using health status data collected from EuroQol Questionnaire (EQ-5D) in a subset of subjects
- To evaluate the impact of FF/VI compared with placebo on healthcare resource utilisation (measured by number of days hospitalized for COPD)

- To evaluate the effect of FF/VI compared with placebo on COPD health status in a subset of subjects using the COPD Assessment Tool (CAT)
- To examine the molecular profiles of blood samples to identify factors that may influence biological and clinical responses to FF/VI compared with placebo and/or associated with the development or progression of COPD or medically related conditions.
- To investigate a composite index to predict mortality

SUMMIT: The Study to Understand Mortality and Morbidity in COPD; FF/VI: Fluticasone Furoate / Vilanterol combination; FEV_1: forced expiratory volume in 1 second; CV: cardiovascular; FF: Fluticasone Furoate; VI: Vilanterol; COPD: chronic obstructive pulmonary disease; FVC: SGRQ-C: St. George's Respiratory Questionnaire for COPD

Table 3: Potential mechanisms related to presence of cardiovascular disease in patients with chronic obstructive pulmonary disease

- Systemic inflammation
- Physical inactivity and deconditioning
- Autonomic imbalance
- Vascular endothelial dysfunction
- Lower arterial compliance
- Arrhythmias
- Thrombogenicity
- Increased afterload resulting from a greater fall in pleural pressure at each inspiration due to impaired lung mechanics in COPD