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LAUNCHING NEW STUDIES

The TORCH (TOwards a Revolution in COPD Health) survival study protocol

The TORCH Study Group

The TORCH (TOwards a Revolution in COPD Health) survival study protocol. The TORCH Study Group. ©ERS Journals Ltd 2004.

ABSTRACT: Only long-term home oxygen therapy has been shown in randomised controlled trials to increase survival in chronic obstructive pulmonary disease (COPD). There have been no trials assessing the effect of inhaled corticosteroids and long-acting bronchodilators, alone or in combination, on mortality in patients with COPD, despite their known benefit in reducing symptoms and exacerbations. The "TOwards a Revolution in COPD Health" (TORCH) survival study is aiming to determine the impact of salmeterol/fluticasone propionate (SFC) combination and the individual components on the survival of COPD patients.

TORCH is a multicentre, randomised, double-blind, parallel-group, placebo-controlled study. Approximately 6,200 patients with moderate-to-severe COPD were randomly assigned to *b.i.d.* treatment with either SFC (50/500 μg), fluticasone propionate (500 μg), salmeterol (50 μg) or placebo for 3 yrs. The primary end-point is all-cause mortality; secondary end-points are COPD morbidity relating to rate of exacerbations and health status, using the St George's Respiratory Questionnaire. Other end-points include other mortality and exacerbation end-points, requirement for long-term oxygen therapy, and clinic lung function. Safety end-points include adverse events, with additional information on bone fractures.

The first patient was recruited in September 2000 and results should be available in 2006. This paper describes the "TOwards a Revolution in COPD Health" study and explains the rationale behind it.

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Morbidity and mortality due to chronic obstructive pulmonary disease (COPD) is continuing to rise [1]. Most COPD treatment focuses on relieving symptoms, but reducing exacerbations, improving health status and possibly improving survival are treatment goals that are equally justifiable from the perspectives of both patients and society. Treatment with the combination of a long-acting β-agonist (LABA) and an inhaled corticosteroid (ICS) improves lung function and symptoms, reduces the incidence of COPD exacerbations and improves health status [2–5], representing an important advance in COPD therapy.

There is accumulating evidence that the progressive course of COPD can be altered. Smoking cessation modifies the progressive development of airflow limitation in COPD [6]. Long-term oxygen therapy for hypoxaemic patients [7, 8] and lung volume reduction surgery in patients with predominantly upper lobe emphysema and limited exercise capacity [9] have delayed death. In addition, some recent observational pharmacoepidemiological findings suggest that ICS, either alone or in combination with a LABA, may also reduce COPD mortality [10, 11].

The "TOwards a Revolution in COPD Health" (TORCH) survival study is designed to prospectively compare the effects of salmeterol and fluticasone propionate in combination (SFC; 50/500 μg), or singly as fluticasone propionate (FP; 500 μg) or salmeterol (50 μg) against placebo *b.i.d. via* the Accuhaler™ (GlaxoSmithKline R&D, Greenford, UK)/Diskus® (GlaxoSmithKline Inc., Research Triangle Park, NC, USA). The primary objective of this study is to determine whether there is a significant reduction in all-cause mortality in COPD patients treated with SFC compared with placebo. This paper describes the protocol design and the approaches taken in this study, as well as the potential biases, which are inherent in a mortality study in COPD. The current authors anticipate that this study will have important implications for the future treatment of COPD patients.

Methods

TORCH study design

This is a 3-yr, multicountry, multicentre, placebo-controlled, double-blind, randomised, parallel-group trial. The study involves a 2-week run-in period, a 3-yr treatment phase and a 2-week follow-up phase. All ICS and inhaled LABAs will be discontinued at entry to the run-in period. Patients will be treated on an outpatient basis and, during treatment, will attend 16 clinic visits at 3-month intervals as shown in figure 1.

Approximately 6,200 patients meeting the European Respiratory Society definitions for COPD [12] have been randomised from ~450 sites to one of the following four treatment groups: placebo (n=1,510), salmeterol (50 μg; n=1,510), FP (500 μg; n=1,510) or SFC (50/500 μg; n=1,510), administered *b.i.d. via* the Accuhaler™/Diskus®. Since smoking status is an important prognostic variable, patients will be stratified according to smoking status (smoker, exsmoker) to help ensure that treatment allocation is

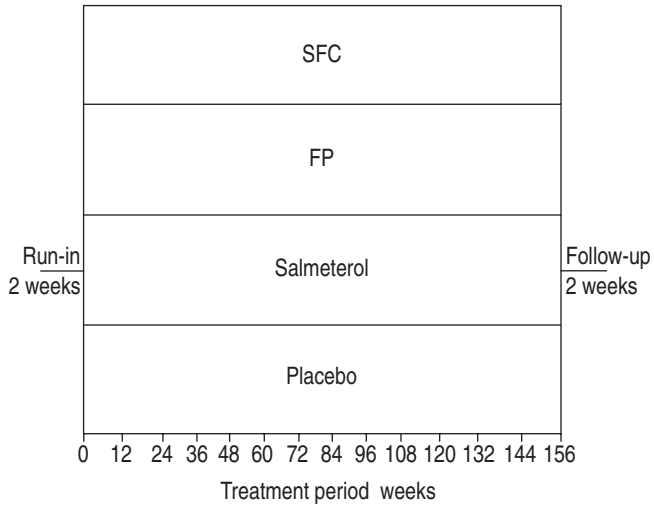

Fig. 1. – Study design of "TOwards a Revolution in COPD Health" (TORCH) survival study. SFC: salmeterol/fluticasone propionate combination; FP: fluticasone propionate.

balanced. Patients who withdraw prematurely from study treatment will still be followed-up through regular contact for 3 yrs from randomisation to determine survival status.

Organisational 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 has been established to protect the ethical and safety interests of the patients. This committee reviews cumulative serious adverse event data every 6 months, in addition to two prespecified interim analyses. An Endpoint Committee has also been established to independently review and categorise the cause of death for each patient where a death has been recorded.

Patient participation

The recruitment goal for the study of 6,040 patients was exceeded. The first patient was recruited in September 2000 and the last in November 2002. Patients were aged 40–80 yrs with a diagnosis of COPD and a smoking history of $\geqslant$10 pack yrs. The inclusion and exclusion criteria are given in Appendix 1. Patients who have an exacerbation of COPD during the run-in period that requires systemic corticosteroid therapy and/or hospitalisation are not eligible for randomisation. Patients are allowed to take any COPD concomitant medication except ICS, long-acting bronchodilators and long-term oral corticosteroids. All patients are offered salbutamol as relief medication.

The study is conducted in accordance with the Declaration of Helsinki [13] and Good Clinical Practice Guidelines [14]. All patients gave written informed consent before participating in the study. The ethics and review boards of all participating institutions have approved this protocol.

Efficacy and health-outcome assessments

The primary end-point measure is all-cause mortality over 3 yrs. Secondary end-points are given in Appendix 2. The other objectives of the study include comparisons of mortality in the SFC group with that seen in the salmeterol and FP groups, and in the salmeterol and FP groups compared with the placebo group. The impact of COPD and its treatment on patients′ health status will be measured by the St. George′s Respiratory Questionnaire and the Euro quality-of-life (QoL) questionnaire at 24-week intervals. Information on COPD exacerbations are collected at each study visit. A moderate exacerbation is defined as one requiring treatment with systemic corticosteroids and/or antibiotics. A severe exacerbation is an exacerbation requiring hospitalisation. Patients with worsening COPD status on study treatment can receive other COPD concomitant medications, but may be withdrawn from the study if there are more than three exacerbations in a 6-month period or, in the investigator′s opinion, the frequency or severity of exacerbations prevents ongoing participation. The reason for withdrawal will be recorded in the case report form (CRF) and patients will be followed-up for the 3 yrs following randomisation. Information on the total use of healthcare resources by patients will be collected during the study through structured interviews at study visits. Study visits will also include measurement of postbronchodilator forced expiratory volume in one second (FEV1).

Survival status

The survival status of each patient is noted at 3-month intervals, until 3 yrs have elapsed since randomisation. This will be the case for all patients, including those who prematurely withdraw from the study. Following a patient′s death, the investigator assigns a cause of death based on information from the attending physician, details given on the death certificate, autopsy findings and any other available clinical evidence entered on a Survival Status Report Form. In addition, independent assessment of cause of death is conducted by the Endpoint Committee at intervals during the study, by review of all available documentation for all deaths prior to assigning causality according to a set of predefined categories. It is this categorisation by the Endpoint Committee that is the primary basis of all subanalyses of specific causes of death, *i.e.* cardiovascular, pulmonary, cancer, other, and unknown. Furthermore, the Committee will evaluate if the death was COPD-related by classifying this point as "no", "unlikely", "possibly", "probably", "yes", or "unknown".

Clinical safety assessments

Each adverse event or concurrent illness that occurs during the study will be documented in the CRF. For any fracture, its anatomical location and whether it is considered traumatic or nontraumatic will also be recorded. An oropharyngeal examination will be carried out at each visit to check for the presence of oral candidiasis. Skeletal, ophthalmic and serum cortisol assessments will also be carried out at selected USA investigational sites.

Statistical analysis

Based on mortality information gathered from the Inhaled Steroids in Obstructive Lung Disease in Europe (ISOLDE) study [15], it is thought that the observed treatment difference between treatment containing ICS and placebo in a population with COPD and FEV1 $\leqslant$60% pred will be $\geqslant$4.3% over 3 yrs. It is also anticipated that the 3-yr placebo mortality rate will be $\geqslant$17%. In this case, the expected treatment difference

would represent a relative reduction in mortality rate of ~25% compared with placebo. Based on this information, the planned sample size is 6,040 patients, assuming a survival rate of 83% on placebo and ⩾87.3% on SFC. The study has 90% power to detect a 4.3% difference in mortality at 3 yrs, with 1,510 patients in each limb of the study and a total of 880 deaths. All subjects will be followed-up for 3 yrs postrandomisation and statistical analysis will be based on the intent-to-treat population. Smoking status, age, sex, and baseline postbronchodilator FEV1 are important variables for prognosis in COPD and analyses will include these variables.

The difference in all-cause mortality, COPD-related mortality and time to first exacerbation will be analysed by means of the log rank test. For all-cause mortality, a Cox proportional hazards regression analysis will also be carried out. Patients with severe exacerbations will be combined with those who die whilst on treatment to form a group of "treatment failures". Rates of survival with respect to this classification will be compared using the log-rank test and Kaplan–Meier plots. All analyses will be performed using the intention-to-treat population.

Discussion

COPD is characterised by progressively deteriorating lung function, accompanied by breathlessness (particularly after physical exertion), cough, sputum production, respiratory failure, and eventually death [12, 16]. The aim of COPD treatment should be to increase lung function, prevent disease progression, decrease symptoms and exacerbations, and improve QoL [17]. Until recently, the approach to therapy has focused mainly on symptomatic relief. However, newer therapies show promise in their potential to improve QoL and reduce serious morbidity, particularly exacerbations of disease and hospital admissions.

The recently updated "Global initiative for chronic Obstructive Lung Disease" guidelines recognise that long-acting bronchodilator therapy is central to the symptomatic management of moderate COPD [17]. LABAs, such as salmeterol, achieve this goal as they provide long-term sustained bronchodilatation without tolerance [2, 3, 18–20]; each dose improves airflow limitation for >12 h [19, 21], reduces breathlessness and exacerbation rate, and is associated with a clinically significant improvement in health status [21]. LABAs exert other effects that may be of clinical relevance [22]. The potential anti-inflammatory and cytoprotective properties of LABAs and the documented effect on exacerbation rate could have a significant impact on patient survival. Whether these effects translate into an observable clinical difference in outcome will be tested as part of the TORCH protocol.

ICS have not been shown to affect decline in FEV1. However, FP does improve lung function and reduce exacerbations, both alone and in combination with salmeterol [15, 23]. None of the studies to date have focused on mortality, nor have been powered sufficiently to do so. However, whilst ISOLDE was not designed to investigate mortality, a reduction in mortality rate in patients treated with FP was seen in a *post hoc* survival analysis [24], which provided a rationale on which to base a definitive mortality study such as TORCH.

Several recent pharmacoepidemiological studies have been used to examine potential long-term effects on mortality from treatment with ICS and LABA. SIN and TU [10] used a large Canadian database and showed that elderly COPD patients gained substantially from treatment with ICS prescribed shortly after a COPD admission. The previous methodology has subsequently been questioned [25]. In a retrospective cohort study from the General Practice Research Database in the UK, patients who used regular salmeterol and/or FP combination therapy (n=1,046) had a significantly greater 3-yr survival advantage over the control patients (n=3,648), with survival rates being 79% and 63%, respectively [11]. A decrease in mortality was observed with increasing number of prescriptions of salmeterol or FP. The highest survival was seen in COPD patients who used both drugs. In a subsequent study limited to COPD patients from the General Practice Research Database with a recent hospital admission, the survival benefit from combined use of salmeterol and FP was greater than that seen for each drug alone [26]. Although these studies were observational, with all the potential drawbacks usual for that design, they do reflect the potential consequences of treating "real-life" COPD with LABA and/or ICS.

Whereas most of the biases present in pharmacoepidemiology are overcome in a randomised controlled trial, a study like TORCH is not without risk of skewed results due to other biases. The main risk will be dilution of effects due to differential withdrawal from the study. In ISOLDE [15], the trial of inhaled steroids and LABAs [3], and a recent study by SZAFRANSKI *et al.* [5] on even more severe patients, withdrawal was significantly greater in the placebo arm than in arms receiving active treatment. Since all active treatments are likely to reduce symptoms as well as exacerbations, the risk of effect dilution due to differential withdrawal seems real.

The TORCH trial has been designed to prospectively test the impact of regular therapy with SFC on survival in patients with COPD. To do this, a number of study issues were considered and debated. Overall mortality was chosen as the primary end-point rather than COPD mortality, because it is not dependent upon coding practice that may vary between countries. Furthermore, it may be very difficult to differentiate reliably between death due to COPD specifically and death where COPD provided a contributory factor. Patients will be stratified according to smoking status. This is in line with the current Committee for Proprietary Medicinal Products COPD guidelines for studies in COPD [27] and will help to ensure that treatment allocation is balanced with respect to this important prognostic variable. SFC at a dose of 50/500 μg *b.i.d.* was chosen for this study, as salmeterol and FP given alone at these doses have previously been shown to improve lung function, symptoms and, in the case of FP, reduce both the incidence and severity of COPD exacerbations. In addition, in order to facilitate cross-study comparisons, the definitions of moderate and severe exacerbations used in the present study are similar to those used in another large worldwide study of combination therapy in COPD [3]. The current authors will attempt to assign the cause of death as accurately as possible using an Endpoint Committee established to independently review and categorise each death, in particular, to determine whether a death was COPD-related. It is recognised that there are ethical reasons why the study may be stopped prematurely should any treatment be substantially more effective in increasing survival than the others, or where safety concerns arise with respect to any treatment. With this in mind, two interim analyses will be conducted during the running of this trial.

The TORCH study may also be able to shed light on areas of controversy regarding the long-term use of ICS in COPD. Patients participating at several of the centres in the USA are undergoing annual bone mineral densitometry, slit lamp-eye examination and assessment of cortisol secretion. This will further improve the ability to use this class of drugs correctly, based on evidence of efficacy and risk of side effects from properly conducted trials.

The "TOwards a Revolution in COPD Health" survival

study will be the largest ever, multicentre, long-term chronic obstructive pulmonary disease study, and the first to investigate the effect of salmeterol/fluticasone propionate combination and its components on chronic obstructive pulmonary disease mortality. A significant effect of salmeterol/fluticasone propionate combination on chronic obstructive pulmonary disease morbidity and mortality would represent a real step forward in the pharmacological management of chronic obstructive pulmonary disease. Even if this does not prove to be the case, the data gathered will shed new light on the natural history of this disorder.

Participants of the TORCH Study Group: Members of the Steering Committee: P. Calverley (UK), B. Celli (USA), G. Ferguson (USA), C. Jenkins (Australia), P. Jones (UK), R. Pauwels (Belgium), N. Pride (UK), J. Vestbo (Denmark), J. Anderson (GlaxoSmithKline, UK), M. Devoy (GlaxoSmithKline, UK). Members of the Safety and Efficacy Data Monitoring Committee: R. Cherniack (USA), T. Similowski (France), J. Cleland (UK), A. Whitehead (UK). Members of the Endpoint Committee: R. Wise (USA), L. McGarvey (UK), M. John (Germany). This manuscript was prepared by J. Vestbo on behalf of the TORCH Steering Committee whose members have all participated in the manuscript process.

Appendix 1: Inclusion and exclusion criteria for the "TOwards a Revolution in COPD Health" (TORCH) survival study

Key inclusion criteria
- Male or female aged 40–80 yrs
- Current or exsmokers with a smoking history of $\geqslant$10 pack yrs
- FEV1 $\leqslant$60% pred, $\leqslant$10% reversibility in predicted FEV1 and a FEV1/FVC ratio $\leqslant$70%
- An established history of COPD

Key exclusion criteria
- Current diagnosis of asthma or respiratory disorders other than COPD
- Chest radiograph indicating diagnosis other than COPD
- Had a lung-volume reduction surgery and/or a lung transplant
- Requirement for LTOT at start of study >12 h·day^{-1}
- Receiving long-term oral corticosteroid therapy
- Serious, uncontrolled disease likely to interfere with the study and/or cause death within the 3-yr study period

Appendix 2: Secondary and other efficacy end-points in the "TOwards a Revolution in COPD Health" (TORCH) survival study

Key secondary end-points
- Reduction in COPD morbidity between SFC and placebo (measured by rate of moderate and severe exacerbations)
- Difference in QoL between SFC and placebo (measured by SGRQ)

Other end-points
- Difference in composite endpoint made up of overall mortality and COPD admissions
- COPD-related mortality
- Requirement for LTOT
- Clinic postbronchodilator FEV1
- Number of withdrawals from treatment
- Health status using Euro QoL questionnaire
- Healthcare utilisation
- Other COPD exacerbation end-points

References

1. Murray C, Lopez A. Alternative projections of mortality and disability by cause 1990–2020: global burden of disease study. *Lancet* 1997; 349: 1498–1504.
2. Mahler DA, Wire P, Horstman D, *et al.* Effectiveness of fluticasone propionate and salmeterol combination delivered *via* the Diskus device in the treatment of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2002; 166: 1084–1091.
3. Calverley P, Pauwels R, Vestbo J, *et al.* Combining salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease. *Lancet* 2003; 361: 449–456.
4. Hanania NA, Darken P, Horstman D, *et al.* The efficacy and safety of fluticasone propionate (250 μg)/salmeterol (50 μg) combined in the Diskus inhaler for the treatment of COPD. *Chest* 2003; 124: 834–843.
5. Szafranski W, Cukier A, Ramirez A, *et al.* Efficacy and safety of budesonide/formoterol in the management of chronic obstructive pulmonary disease. *Eur Respir J* 2003; 21: 74–81.
6. Anthonisen NR, Connett JE, Murray RP, for the Lung Health Study Research Group. Smoking and lung function of Lung Health Study participants after 11 years. *Am J Respir Crit Care Med* 2002; 166: 675–679.
7. Long term domicilary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. Report of the Medical Research Council Working Party. *Lancet* 1981; 1: 681–686.
8. Crockett AJ, Cranston JM, Moss JR, Alpers JH. Survival on long-term oxygen therapy in chronic airflow limitation: from evidence to outcomes in the routine clinical setting. *Intern Med J* 2001; 31: 448–454.
9. Fishman A, Martinez F, Naunheim K, *et al.* National Emphysema Treatment Trial Research Group. A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. *N Engl J Med* 2003; 348: 2059–2073.
10. Sin D, Tu J. Inhaled corticosteroids and the risk of mortality and readmission in elderly patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001; 164: 580–584.
11. Soriano JB, Vestbo J, Pride NB, Kiri V, Maden C, Maier WC. Survival in COPD patients after use of salmeterol and/or fluticasone propionate in general practice. *Eur Respir J* 2002; 20: 819–825.
12. Siafakas N, Vermeire P, Pride N, *et al.* Optimal assessment and management of chronic obstructive pulmonary disease (COPD). The European Respiratory Society Task Force. *Eur Respir J* 1995; 8: 1398–1420.
13. World Medical Organisation. Declaration of Helsinki. *BMJ* 1996; 313: 1448–1449.
14. Directive 2001/20/EC of the European parliament and of the council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the member states relating to the implementation of good clinical practice in the conduct of clinical trails on medicinal products for human use. *Official Journal of the European Communities* 2002; 1.5: 121–134.
15. Burge P, Calverley P, Jones P, *et al.* Randomised, double-blind, placebo-controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. *BMJ* 2000; 320: 1297–1303.
16. Standards for the diagnosis and care of patients with chronic

obstructive pulmonary disease (COPD) and asthma. *Am Rev Respir Dis* 1987; 136: 225–244.
17. Fabbri L, Hurd SS, for the GOLD Scientific Committee. Global strategy for the diagnosis, management and prevention of COPD: 2003 update. *Eur Respir J* 2003; 22: 1–2.
18. Mahler D, Donohue J, Barbee R, *et al.* Efficacy of salmeterol xinafoate in the treatment of COPD. *Chest* 1999; 115: 957–965.
19. Cazzola M, Matera M, Santangelo G, *et al.* Salmeterol and formoterol in partially reversible severe chronic obstructive pulmonary disease: a dose-response study. *Respir Med* 1995; 89: 357–362.
20. Celik G, Kayacan O, Beder S, *et al.* Formoterol and salmeterol in partially reversible chronic obstructive pulmonary disease: a crossover, placebo-controlled comparison of onset and duration of action. *Respiration* 1999; 66: 434–439.
21. Jones P, Bosh T. Quality of life changes in COPD patients treated with salmeterol. *Am J Respir Crit Care Med* 1997; 155: 1283–1289.
22. Johnson M, Rennard S. Alternative mechanisms for long-acting beta$_2$-adrenergic agonists in COPD. *Chest* 2001; 120: 258–270.
23. Paggiaro P, Dahle R, Bakran I, Frith L, Hollingworth K. Multicentre randomised placebo-controlled trial of inhaled fluticasone propionate in patients with chronic obstructive pulmonary disease. *Lancet* 1998; 351: 773–780.
24. Waterhouse JC, Fishwick D, Burge PS, Calverley PMA, Anderson JA, on behalf of the ISOLDE Trial group. What caused death in the ISOLDE study? *Eur Respir J* 1999; 14: Suppl. 30, 387S.
25. Suissa S. Effectiveness of inhaled corticosteroids in COPD: immortal time bias in observational studies. *Am J Respir Crit Care Med* 2003; 168: 49–53.
26. Soriano JB, Kiri VA, Pride NB, Vestbo J. Inhaled corticosteroids with/without long-acting ß-agonists reduce the risk of rehospitalization and death in COPD patients. *Am J Respir Med* 2003; 2: 67–74.
27. Committee for Proprietary Medicinal Products (CPMP). Points to consider on clinical investigation of medicinal products in the chronic treatment of patients with chronic obstructive pulmonary disease (COPD). 1999; CPMP/EWP/562/98. http://www.emea.eu.int/pdfs/human/ewp/056298en.pdf. Date updated: 19 May 1999.