Fast onset of action of glycopyrronium compared with tiotropium in patients with moderate to severe COPD — A randomised, multicentre, crossover trial

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Abstract

Background: Long-acting bronchodilators, including anticholinergics glycopyrronium and tiotropium, are central to symptomatic management of chronic obstructive pulmonary disease (COPD). In patients with moderate to severe COPD, glycopyrronium has demonstrated comparable efficacy to open-label and single-blinded tiotropium, but with faster onset of bronchodilation. The FAST study assessed the efficacy of glycopyrronium compared with tiotropium in serial spirometry and body plethysmography assessments to further characterize the earlier onset of action associated with glycopyrronium.

Methods: In this German multicentre, randomised, double-blinded, double-dummy, cross-over study, patients with moderate-to-severe COPD received single-dose of glycopyrronium 44 μg and tiotropium 18 μg via the Breezhaler® and Handihaler® devices, respectively. Primary objective was to demonstrate superiority of glycopyrronium over tiotropium in terms of improvement in forced expiratory volume in 1 s as assessed by the area under the curve from 0 to 2 h (FEV1 AUC0-2h). Secondary endpoints were functional residual capacity (FRC), residual volume (RV), inspiratory capacity (IC), and specific airway resistance (sRaw), all measured by body plethysmography.

Results: Of the 152 patients randomised, 99.3% completed the study. After inhalation of the single dose, glycopyrronium demonstrated superiority over tiotropium in early bronchodilation as assessed by improvement in FEV1 AUC0-2h (least squares mean treatment difference = 37 mL; 95% CI: 16, 59 mL; p < 0.01) and FEV1 at 15 min post-dose (least square mean treatment difference = 36 mL; 95% CI: 14, 58 mL; p < 0.01). Both treatments showed similar improvements in FRCpleth, RV, and IC. Glycopyrronium showed statistically significant improvement in sRaw compared with tiotropium over the first 90 min after dosing, with the difference of 0.184 kPa × s at 90 min post-dose (95% CI: 0.315,0.054 kPa × s; p < 0.01).

Conclusions: Glycopyrronium was superior to tiotropium in terms of early bronchodilation. Although both glycopyrronium and tiotropium showed similar improvements in static lung volume parameters, glycopyrronium reduced specific airway resistance faster than tiotropium, which could in part explain the earlier FEV1 response seen with glycopyrronium.

Trial registration: ClinicalTrials.gov NCT01922271.

1. Background

Chronic obstructive pulmonary disease (COPD) is a progressively debilitating respiratory disease affecting more than 400 million people worldwide [1] and 2.7 million in Germany [2]. Long-acting bronchodilators, including long-acting muscarinic antagonists (LAMAs), are central to the management of symptoms in...
patients with COPD [3]. Glycopyrronium 50 μg once daily (44 μg delivered dose from the Breezhaler® dry power inhaler [DPI]) is an inhaled LAMA, developed for maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD [4].

In patients with moderate to severe COPD, treatment with once-daily glycopyrronium resulted in significant improvement in lung function, breathlessness, health status and reduction in rescue medication use compared with placebo and demonstrated a comparable safety profile to other LAMAs [5]. Previous Phase III clinical trials have shown comparable efficacy and safety of glycopyrronium to another LAMA, tiotropium (open-label and blinded); however, compared with tiotropium, glycopyrronium showed faster onset of action resulting in better early bronchodilation during the first 4 h post-dose [5,6].

While spirometry is considered the gold standard to measure airflow limitation in patient with COPD [3], body plethysmography can provide additional information regarding airway resistance and lung hyperinflation [7,8]. Here we present the results from the FAST study, which compared the efficacy of glycopyrronium and tiotropium in a double-blind crossover trial using serial spirometry and body plethysmography measurements to further characterize the early onset of bronchodilation with glycopyrronium.

2. Methods

2.1. Study aim and design

This study aimed to assess the early bronchodilation of glycopyrronium (Seebri®; 44 μg; Novartis AG, Switzerland) compared with tiotropium (Spiriva®; 18 μg; Boehringer Ingelheim GmbH, Germany) in patients with moderate to severe COPD. The study was a Phase IV randomised clinical trial using a 2 period crossover design in 15 secondary-care centres in Germany (ClinicalTrial.gov identifier: NCT01922271). Randomised single-dose administration was double-blind and double-dummy to account for the necessary use of the different proprietary DPIs in clinical use: Breezhaler® (glycopyrronium; Novartis AG) and Handihaler® (tiotropium; Boehringer Ingelheim GmbH).

The primary outcome was improvement in forced expiratory volume in 1 s as assessed by the area under the curve from 0 to 2 h (FEV1 AUC [0–2]). Secondary outcomes included evaluation of lung function responses in terms of FEV1 measured at 15 min post-dose and sequential post-dose measurements of specific airway resistance (sRaw) and lung volume parameters from body plethysmography. Exploratory outcomes were further comparisons between treatments in spirometry parameters and the number of patients with peak inspiratory capacity (IC) increments exceeding predetermined thresholds (as an indicator of relief from hyperinflation). Safety parameters were routinely assessed.

The study was approved by ethics committees at the participating centres, and was conducted in accordance with Declaration of Helsinki and Good Clinical Practice guidelines. To participate in the study, all patients were required to provide written informed consent.

The study consisted of the pre-screening period (Visit 1), the second screening visit (Visit 2) and first and second dose visits (Visit 3 and 4, respectively, Fig. 1).

2.2. Patients

Enrolment included both male and female adults aged 40 years and over with a clinical diagnosis of stable COPD or moderate to severe COPD (GOLD 2012 criteria [9]) and a smoking history of at least 10 pack years. Both current and ex-smokers were included. Inclusion depended on confirmed post-bronchodilator spirometry criteria of FEV1 ≥30% and <70% of the predicted normal and FEV1/forced vital capacity (FVC) < 0.70 as measured on Visit 2 (screening, Day –3). Patients could voluntarily withdraw from the study for any reason at any time.

Patients were excluded according to specified criteria and no additional exclusion criteria were permitted by the investigator to maximize representation of all eligible patients. Key exclusion criteria included history of clinical significant disease other than COPD that could interfere with the assessments (including asthma, some cardiovascular diseases, and some diabetic conditions), severe COPD exacerbations requiring treatment and/or hospitalization in the 6 weeks prior to screening, history of malignancy within the past 5 years, and history of hypersensitivity to any of the study drugs.

Exclusion criteria also included concomitant or recent use of prohibited medications. COPD-related medications requiring washout prior to run-in included muscarinic antagonists, β2 agonists, parental or oral corticosteroids, oral phosphodiesterase-IV inhibitor or xanthines. Patients taking inhaled corticosteroids in fixed-dose combination were permitted to be switched to monotherapy with inhaled corticosteroid at a stabilised dose. Medications permitted only if they were stable for appropriate periods (as described in the protocol) prior to screening included selective serotonin reuptake inhibitors, inhaled or intra-nasal corticosteroids and H1-antagonists. Inactivated vaccines were also administered prior to 48 h of the trial. Other prohibited medications and procedures with known potential to interact with study medication or influence outcomes were reviewed for appropriate cessation prior to run-in.

Each patient was provided with an inhaler containing rescue medication (salbutamol) for use as required. No other rescue treatment was permitted and patients were instructed to abstain from using the permitted rescue medication within 6 h of the start of spirometry measurements, unless absolutely necessary (in the event of which, the visit was rescheduled for the following day).

During washout at crossover (between visits 3 and 4), only stable permitted—medications and the provided rescue medication were allowed; no study drug was dispensed to the patients.

2.3. Investigational treatments

Investigational treatments were either glycopyrronium 44 μg capsules delivered via the Breezhaler® single-dose DPI or tiotropium 18 μg capsules delivered via the Handihaler® single-dose DPI. As different devices were necessarily used to deliver active drugs according to licensed formulation, patients inhaled from both devices on both single-dose visits (Visits 3 and 4), with one of the devices containing an unidentifiable placebo capsule, according to the double-dummy design. The active treatment inhaler was switched on the second single-dose visit (Visit 4). Active treatments were administered using their licensed inhalers only and the use of spacers was not permitted at any time during the study.

All therapies and placebo were supplied by Novartis and prepared by unblinded personnel to be ready-to-inhale. The same unblinded personnel also supervised the administration from inhalers by the patient. Patients, investigators and data analysts were blinded to the identity of treatments given until database lock.

2.4. Schedule of study

At Visit 1 (ranging from Day –18 to Day –10), baseline demographics (including the questionnaires for modified Medical Research Council [mMRC] dyspnoea scale [10] and COPD Assessment Test [CAT] score [11]) were collected and adjustments (“washout”) to COPD therapy made where possible to be compliant
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