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The efficacy of tiotropium administered via Respimat® Soft Mist™ Inhaler or HandiHaler® in COPD patients☆

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Summary
Background: Tiotropium, a once daily inhaled anticholinergic delivered via HandiHaler®, provides bronchodilation for >24 h and improves patient-centred outcomes. The Respimat® Soft Mist™ Inhaler (SMI), a novel, propellant-free inhaler, has been developed and proposed as an alternative delivery device for use with tiotropium.
Methods: In a pre-specified, pooled analysis of two 30-week, double-blind, double-dummy, crossover studies, 207 patients with Chronic Obstructive Pulmonary Disease (COPD) were randomised to receive once daily tiotropium 5 μg or 10 μg (aqueous solution delivered via Respimat SMI), tiotropium 18 μg (inhalation powder via HandiHaler) or placebo. The primary endpoint was trough forced expiratory volume in 1 s (FEV_1) response. Forced vital capacity (FVC), peak expiratory flow rate (PEFR), rescue medication use, safety and pharmacokinetics (in a subgroup of patients) were also assessed.
Results: Both tiotropium doses delivered by Respimat SMI were significantly superior to placebo and non-inferior to tiotropium 18 μg HandiHaler on the primary endpoint (all $p < 0.0001$). All active treatments were significantly superior to placebo (all $p < 0.0001$) and both doses of tiotropium Respimat SMI were non-inferior to tiotropium 18 μg HandiHaler on the secondary spirometry variables and rescue medication use. The systemic exposure was similar between tiotropium 5 μg Respimat SMI and tiotropium 18 μg HandiHaler but was higher for tiotropium 10 μg Respimat SMI. All active treatments were well tolerated.

☆ Co-ordinating centres of this multicentre study were the Atrium Medisch Centrum, Heerlen and Spartanburg Clinical Research, USA.

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Conclusions: Tiotropium 5 μg Respimat SMI is comparable with tiotropium 18 μg HandiHaler in terms of efficacy, pharmacokinetics and safety. Respimat SMI is an effective alternative, multi-dose delivery device for tiotropium.
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Introduction

A new generation, propellant-free inhaler, known as the Respimat® Soft Mist™ Inhaler (SMI) has been developed for delivering drugs to the lungs in COPD patients.[1] This device is unique in that it uses mechanical energy, in the form of a spring, to generate a fine, slow-moving cloud (the Soft Mist™) for inhalation. Respimat SMI also has a number of benefits. Most notably, it is simple to coordinate and the delivered dose is independent of inspiratory effort; it is therefore not affected by the breathing manoeuvre problems inherent with some other devices, so it is suitable for all patients to use.[2–4]

Previously reported studies have shown that the delivery of ipratropium bromide/fenoterol hydrobromide via Respimat SMI is as safe and effective as delivery from an established metered-dose inhaler (MDI).[5,6] However, Respimat SMI has primarily been developed as an alternative delivery device for use with tiotropium, an established anticholinergic that provides prolonged M_3 receptor blockade. The lung function improvements associated with tiotropium HandiHaler® (the usual delivery vehicle) have been well established in clinical trials of COPD patients.[7–12]

Short-term studies of Respimat SMI have been favourable in a randomised, double-blind-within-device, parallel-group, dose-ranging study, tiotropium 1.25–20 μg Respimat SMI, tiotropium 18 μg HandiHaler or placebo were administered to 202 COPD patients for 3 weeks.[13] This study showed that tiotropium 5 μg Respimat SMI and tiotropium 18 μg HandiHaler improved lung function to a statistically significantly greater extent than placebo. The primary aim of the current studies was to demonstrate non-inferiority of lung function response to either tiotropium 5 μg or 10 μg Respimat SMI compared with tiotropium 18 μg HandiHaler in patients with COPD after 4-week treatment periods.

Methods

Study design

This was a pre-specified pooled analysis of two identical 30-week, multicentre, randomised, placebo-controlled, double-blind, double-dummy, crossover studies. These trials were designed to assess the efficacy and tolerability of two doses of tiotropium (5 μg or 10 μg) delivered via Respimat SMI (Boehringer Ingelheim, Ingelheim am Rhein, Germany) and one dose of tiotropium (18 μg) delivered via HandiHaler (Boehringer Ingelheim, Ingelheim am Rhein, Germany) in patients with COPD. One study (#205.249) was conducted at 11 centres in the United States (10 centres) and Canada (one centre), and one study (#205.250) was conducted at two centres, one in the Netherlands and one in Belgium.[14] The studies were conducted in accordance with the Declaration of Helsinki (1996), and were approved by the relevant Independent Ethics Committees.

Following screening and a 2-week run-in period, eligible patients were randomised to four 4-week treatment periods (Fig. 1). The treatments were tiotropium 5 μg (two actuations of 2.5 μg) Respimat SMI plus one inhalation of placebo HandiHaler; tiotropium 10 μg (two actuations of 5 μg) Respimat SMI plus one inhalation of placebo HandiHaler; tiotropium 18 μg HandiHaler plus two inhalations of placebo Respimat SMI; or two inhalations of placebo Respimat SMI plus one inhalation of placebo HandiHaler. All doses were administered in the morning between 07:00 and 10:00 h, and Respimat SMI doses were administered before the HandiHaler dose. Each treatment period was separated by a 4-week washout period.

Subjects

Patients were males or females aged $\geq$40 years with a diagnosis of COPD (pre-bronchodilator forced expiratory volume in 1 s [FEV_1] $\leq$ 60% predicted normal[15] and FEV_1/forced vital capacity [FVC] $\leq$ 70%) and were current or ex-smokers with >10 pack-year smoking history. Patients with significant diseases other than COPD, or those with a history of asthma or allergic rhinitis, were excluded, as were pregnant or nursing women and pre-menopausal women not using adequate contraception. Patients with a respiratory infection or COPD exacerbation were also excluded. Patients taking regular daytime oxygen therapy, β-blocker medications, cromolyn sodium, nedocromil sodium, anti-leukotrienes or oral corticosteroids at unstable doses were excluded. All patients provided written informed consent to participate.

Medication restrictions

Prior to the screening visit, short-acting anticholinergics and short-acting β agonists were not permitted for 8 h, long-acting β agonists were not permitted for 48 h, and short-acting theophylline was not permitted for 24 h. Patients were required to stop using tiotropium HandiHaler 4 weeks prior to inclusion. Some medications were allowed during the study if they were stabilised for at least 6 weeks prior to and during the study. These included oral and inhaled corticosteroids, mucolytic agents and salbutamol, which could be used by the patients as rescue medication during each of the 4-week treatment periods. Inhaled short-acting or long-acting β agonists were allowed during the washout periods, but were not permitted for 8 h and 48 h, respectively, prior to clinic visits, and short-acting theophylline could be used as long as there was a 24-h washout prior to clinic visits.

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