Does a single dose of the phosphodiesterase 4 inhibitor, cilomilast (15 mg), induce bronchodilation in patients with chronic obstructive pulmonary disease?

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Abstract

Maintenance treatment with PDE\textsubscript{4} inhibitor cilomilast improves FEV\textsubscript{1} in chronic obstructive pulmonary disease (COPD) patients. We investigated the acute bronchodilating effects of a single dose of cilomilast with or without concomitant administration of inhaled salbutamol and/or ipratropium bromide in 21 patients with COPD (mean (SD) age 64 (8.1) y, post-salbutamol FEV\textsubscript{1} 47.7 (13.2) %predicted). FEV\textsubscript{1} was measured before and up to 8 hourly intervals after intake of placebo, cilomilast, or cilomilast in combination with inhaled salbutamol 400 µg and/or ipratropium bromide 80 µg. Maximum increase in FEV\textsubscript{1} from pre-dose baseline was calculated after each treatment and differences between treatment arms were analyzed by ANOVA. The mean (SEM) maximum increase in FEV\textsubscript{1} was 139.6 (18.5) ml following cilomilast and 151.5 (18.5) ml following placebo (95% C.I. for mean difference between cilomilast and placebo: 2.67.3, 43.6 ml). Furthermore, combined treatment of cilomilast with salbutamol or ipratropium resulted in a maximum increase in FEV\textsubscript{1} of 280.7 (25.6) and 297.0 (25.9) ml, respectively, while this was 379.0 (24.6) ml following cilomilast with both salbutamol and ipratropium (p < 0.01). We conclude that a single dose of cilomilast does not produce acute bronchodilation in patients with COPD who otherwise respond to inhaled bronchodilators. Our results implicate that the change in lung function seen after long-term treatment with cilomilast is not the result of acute bronchodilation in patients with COPD.

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1. Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by cough, sputum production, dyspnea and airflow limitation that is not fully reversible [1]. The pathologic findings within the Airways underlying the progressive airflow limitation in COPD include an increased cell influx of CD8\textsuperscript{+} T lymphocytes together with increased smooth muscle mass, when compared to smokers without COPD [2,3].

At present, the recommended treatment of COPD is relief of symptoms with bronchodilators, either when needed or on a regular basis [1]. In addition, many patients with COPD are treated with inhaled corticosteroids (ICS). While ICS may provide an improvement in exacerbation rate [4], such treatment does not seem to influence the long-term progressive decline in lung function [5–7]. Therefore, new drugs are needed to improve the control of symptoms and to prevent the progression of COPD.

Cilomilast (Ariflo\textsuperscript{\textregistered}) is a second generation, oral phosphodiesterase 4 (PDE\textsubscript{4}) inhibitor currently under development for the treatment of COPD. The advantage of cilomilast over non-specific PDE inhibitors such as theophylline and previous PDE\textsubscript{4} inhibitors such as zardaverine (Rolipram\textsuperscript{\textregistered}) is a more favorable therapeutic index of cilomilast (8). It has recently been shown in patients with poorly reversible COPD that 6 weeks treatment with cilomilast (15 mg twice daily) improves FEV\textsubscript{1} by 160 ml [9]. However, it is not
known whether cilomilast provides acute bronchodilation in patients with COPD, or its time course.

The aim of this study was to estimate the difference in first-dose bronchodilation between a single dose of cilomilast (15 mg) and placebo in patients with COPD during 8 h after administration. Furthermore, most patients with COPD use short-acting bronchodilators for on demand relief of symptoms. Therefore, the secondary aim of this study was to estimate the difference in bronchodilation between a single dose of cilomilast and a single dose of cilomilast administered in conjunction with inhalation of (a) salbutamol 400 μg, (b) ipratropium 80 μg and (c) salbutamol 400 μg and ipratropium 80 μg in these patients with COPD.

2. Methods

2.1. Patients

Twenty-one clinically stable patients with a diagnosis of COPD [10] volunteered to participate in the study. Patients had to fulfill the following inclusion criteria: aged between 40 and 80 y, smoking history at least 10 packyears, pre-bronchodilator FEV₁/FVC ≤ 0.7, post-bronchodilator FEV₁ 30–70% predicted [11], fixed airways obstruction as defined by <15% and/or <200 ml increase in FEV₁ and/or FEV₁ < 75% predicted after administration of 400 μg salbutamol, dyspnea during daily activities in the week prior to inclusion and transcutaneous oxygen saturation ≥90%. Usage of regular ICS and on demand short-acting bronchodilators or anticholinergics were allowed during the study, whereas long-acting bronchodilators were discontinued for the duration of the study. None of the patients had suffered from an exacerbation of COPD, nor used oral glucocorticosteroids or xanthines in the 4 weeks prior to inclusion. The study was approved by the Medical Ethics Committee of the Leiden University Medical Centre. Written informed consent was obtained from all patients.

2.2. Design

The study consisted of 4 parts within a period of 8 weeks: run-in (visit 1 and 2); period 1, consisting of double-blind, cross-over treatment with cilomilast or placebo (visit 3 and 4); period 2, consisting of open label treatment with cilomilast and co-administration with other bronchodilators (visits 5, 6 and 7); and safety follow-up (visit 8, Fig. 1). At the first visit in- and exclusion criteria were checked. To that end, medical history, physical examination and spirometry with reversibility in FEV₁ to 400 μg salbutamol were determined, followed by assessment of vital signs (blood pressure and heart rate), 12-lead ECG recording, urinalysis and routine hematology and clinical chemistry evaluation. At the second visit, FEV₁ reversibility to 80 μg ipratropium was measured and assessments of vital signs and 12-lead ECG were repeated.

In period 1, patients received randomized, double-blind treatment with one tablet of cilomilast (15 mg) or placebo. FEV₁ was measured pre-dose and at 1, 2, 3, 4, 5, 6, 7 and 8 h post-treatment. In addition, safety measurements of vital signs and 12-lead ECG were performed pre-dose and at 1, 4, and 8 h post-treatment. Blood samples for pharmacokinetic analysis of cilomilast plasma levels were drawn pre-dose and at 1, 2, 3, 4, 6, 8 and 24 h post-treatment. Adverse events were monitored at 1, 3, and 8 h post-treatment.

In period 2, all patients received one tablet open-label cilomilast (15 mg) in combination with inhalation of open-label salbutamol 400 μg, ipratropium 80 μg or salbutamol 400 μg and ipratropium 80 μg. The order of inhaled medications was randomized over the three visits in this period. Assessment of FEV₁, safety measurements and adverse events were the same as during period 1, blood for pharmacokinetic analysis was drawn pre-dose and at 1, 2, 3, 4, 6, 8 and 24 h post-treatment.

At the safety follow-up visit, vital signs, 12-lead ECG and urinalysis were performed. Blood for routine analysis of hematology and clinical chemistry was withdrawn at visit 1, 3, 5, and 8.

![Fig. 1. Design of the study. Period 1 consisted of double-blind, randomized, cross-over treatment with cilomilast or placebo. Period 2 consisted of open label, three part randomized, cross-over administration of cilomilast together with either salbutamol, or ipratropium or both. On the visits during period 1 and 2 the following measurements were performed: FEV₁ pre-dosing and at 8 hourly intervals thereafter; blood sampling for determination of cilomilast levels in plasma before and at 1, 2, 3, 4, 6 and 8 h after administration of medication (on visits 3 and 4 of period 1 also at 24 h post-dosing); ECG and blood pressure/heart rate before and at 1, 4 and 8 h after administration of medication; adverse events monitored at 1, 3, and 8 h post-dosing.](image-url)
Patients were asked to refrain from short-acting β2-agonists and anticholinergics as of from 4 h before each study visit. Caffeine containing food and beverages were not allowed on visits 3–7.

2.3. Pulmonary function tests

Measurements of FEV$_1$ were performed in triplicate at each timepoint according to standards [12] using a pneumotachograph (PDS Instrumentation, Louisville, CO, USA). Measurements were compared to reference values of Crapo et al. [11].

Reversibility in FEV$_1$ was established by measuring FEV$_1$ before and at 30 min after inhalation of salbutamol 400 μg or ipratropium 80 μg (visit 1 and 2, respectively). Reversibility was calculated as the difference between post- and pre-bronchodilator FEV$_1$. At visits 1, 2, 5, 6, and 7, salbutamol and/or ipratropium were administered by pressurized metered dose inhaler connected to an aerosol chamber®.

2.4. Safety assessments

Heart rate, systolic and diastolic blood pressure were measured using a dinamap (Critikon Inc., Tampa, Fl, USA) with the patient in supine position. Twelve-lead ECGs were recorded using a Cardiovit CS6/12 (CardioKinetics Ltd, Schiller AG, Baar, Switzerland). Blood for routine evaluation of hematology and clinical chemistry was collected in tubes containing EDTA and serum-gel clotting activator, respectively. Urinalysis for blood, glucose, protein and ketoses was performed by dip-stick.

2.5. Pharmacokinetic assessments

Blood was collected in EDTA containing tubes and immediately placed on ice. Within 1 h, plasma was separated by centrifugation (3000 rpm, 15 min). Samples were stored in polypropylene tubes at −20 °C until measurement of cilomilast levels. Plasma concentrations of cilomilast were quantified using a method based on protein precipitation followed by high performance liquid chromatography with tandem mass spectrometric detection (lower limit of detection: 10.0 ng/ml).

2.6. Statistical analysis

The primary endpoint was maximum increase in FEV$_1$ from baseline between 0 and 8 h post-treatment, expressed in millilitre. As secondary endpoint, the area under the curve (AUC) for increase in FEV$_1$ from baseline between 0 and 8 h after administration of medication, divided by 8 was calculated and expressed in ml/hr. The primary comparison was difference in these two outcomes between cilomilast and placebo. Data were analyzed using an analysis of variance (ANOVA) appropriate to the two-period cross-over design, including effects sequence (cilomilast-placebo, placebo-cilomilast), subject, period and regimen (cilomilast or placebo), with baseline FEV$_1$ as covariate in the model. The difference between cilomilast and cilomilast plus bronchodilators was the secondary comparison of interest. Data were analyzed using an ANOVA including effects subject and regimen with baseline FEV$_1$ fitted as a covariate. It should be noted that cilomilast alone was always received in period 1, so the contrasts with cilomilast plus bronchodilators are confounded with period. Point estimates of mean difference between each of the regimens and 95% confidence intervals (CI) were computed from the residual variance from the ANOVA.

3. Results

Of the 21 included patients, 19 completed the study successfully. One patient was withdrawn after visit 2 because of a transient ischemic attack and therefore excluded from all summaries and statistics. One patient was withdrawn from the study after visit 5 due to an exacerbation of COPD, requiring treatment with antibiotics and oral glucocorticosteroids. The latter patient contributed to the analysis of the run-in visits (visit 1 and 2), period 1 (visit 3 and 4) and cilomilast plus salbutamol and ipratropium (visit 5). Pharmacokinetic results showed that one patient received placebo tablets on both visits of period 1 and was excluded from all summaries and statistics. Patient demographics together with reversibility in salbutamol or ipratropium are summarized in Table 1.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patient demographics</th>
<th>Mean (SD)</th>
</tr>
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<tbody>
<tr>
<td>Male:female (n)</td>
<td>15:4</td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>64 (8.1)</td>
<td></td>
</tr>
<tr>
<td>Pre-salbutamol FEV$_1$ (l)</td>
<td>1.34 (0.42)</td>
<td></td>
</tr>
<tr>
<td>Pre-salbutamol FEV$_1$ (%predicted)</td>
<td>42.4 (13.7)</td>
<td></td>
</tr>
<tr>
<td>Post-salbutamol FEV$_1$ (l)</td>
<td>1.51 (0.42)</td>
<td></td>
</tr>
<tr>
<td>Post-salbutamol FEV$_1$ (%predicted)</td>
<td>47.7 (13.2)</td>
<td></td>
</tr>
<tr>
<td>Reversibility salbutamol (ml)</td>
<td>161 (109)</td>
<td></td>
</tr>
<tr>
<td>Reversibility ipratropium (ml)</td>
<td>256 (122)</td>
<td></td>
</tr>
<tr>
<td>Patients using ICS (n)</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Daily dose ICS (μg)</td>
<td>646.7 (277.4)</td>
<td></td>
</tr>
<tr>
<td>Patients using long-acting bronchodilators prior to inclusion (n)</td>
<td>15</td>
<td></td>
</tr>
</tbody>
</table>

3.1. Cilomilast versus placebo

The changes in FEV$_1$ relative to baseline over the 8 h after administration of either cilomilast or placebo are shown in Fig. 2. The mean (SEM) maximum increase in FEV$_1$ was 139.6 (18.5) ml following cilomilast and 151.5 (18.5) ml following placebo treatment, which was not statistically different between the treatments. The mean difference in
maximum increase in FEV$_1$ (95% CI) between cilomilast and placebo treatment was $-11.9 \ (267.3, \ 43.6)$ ml (Table 2). Furthermore, the AUC for increase in FEV$_1$ was not statistically different between cilomilast and placebo (95% CI for mean difference $-49.1, \ 39.7$).

### 3.2. Cilomilast versus cilomilast plus bronchodilators

Fig. 2 also shows the changes in FEV$_1$, relative to baseline, during the 8 h after the use of cilomilast together with other bronchodilators. Following treatment with cilomilast in combination with salbutamol or ipratropium, mean (SEM) FEV$_1$ increased with a maximum of 280.7 (25.6) and 297.0 (25.9) ml compared to baseline, respectively. Treatment with cilomilast with salbutamol and ipratropium resulted in a maximum increase in FEV$_1$ of 379.7 (24.6) ml. The maximum increase in FEV$_1$ and AUC for increase in FEV$_1$ after administration of each of the combinations of cilomilast with bronchodilators were significantly greater as compared to that after administration of cilomilast alone (Table 2, $p < 0.01$).

### 3.3. Adverse events

During the study, a total of 57 adverse events occurred which were reported by 16 patients. Of these adverse events, 33 (57.9%) were considered not to be related to the study medication, 17 (29.8%) were unlikely to be related and 7 (12.3%) were suspected to be related to intake of the study medication. Most commonly reported adverse events were dizziness (2 following cilomilast treatment versus 1 following placebo treatment), headache (2 versus 0), dyspnea (1 versus 1), and agitation (1 versus 0).

### 3.4. Safety

No changes were observed in hematologic and clinical chemistry laboratory results throughout the study (data not shown). In addition, corrected QT interval, heart rate, diastolic and systolic blood pressure remained stable during and between each of the study days.

### 3.5. Pharmacokinetics of cilomilast

The maximum (range) concentration of cilomilast in plasma was 1510 (1025–2393) ng/ml, which was reached at a median (range) of 1.98 (0.88–4.25) h following administration of cilomilast alone. The pharmacokinetics of cilomilast did not differ between each of the treatment arms (Fig. 3).

### 4. Discussion

The results of this study show that in patients with moderate COPD, FEV$_1$ does not improve within the first 8 h following administration of a single dose of the PDE$_4$ inhibitor cilomilast (15 mg). Furthermore, the improvement

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**Table 2**

<table>
<thead>
<tr>
<th></th>
<th>Maximum increase in FEV$_1$ (ml)</th>
<th>AUC for increase in FEV$_1$ (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cilomilast vs placebo</td>
<td>$-11.9 \ (267.3, \ 43.6)$</td>
<td>$-4.7 \ (49.1, \ 39.7)$</td>
</tr>
<tr>
<td>Cilomilast + S vs cilomilast</td>
<td>132.1 (59.2, 205.0)*</td>
<td>88.6 (32.5, 144.6)*</td>
</tr>
<tr>
<td>Cilomilast + I vs cilomilast</td>
<td>148.4 (74.5, 222.3)*</td>
<td>116.4 (59.5, 173.3)*</td>
</tr>
<tr>
<td>Cilomilast + S + I vs cilomilast</td>
<td>231.1 (159.6, 302.6)*</td>
<td>169.5 (114.5, 224.5)*</td>
</tr>
</tbody>
</table>

S: salbutamol 400 μg, I: ipratropium 80 μg. *: $p < 0.01$. 

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Fig. 2. Mean (SEM) change in FEV$_1$ (ml) from baseline following 8 h after administration of placebo (closed circles), cilomilast (closed squares), cilomilast plus salbutamol (open squares), cilomilast plus ipratropium (open triangles) and cilomilast plus salbutamol plus ipratropium (open circles).
in FEV₁ following administration of cilomilast in combination with salbutamol and/or ipratropium is significantly different from that following cilomilast alone, in these patients with COPD. This indicates that a single dose of cilomilast does not produce acute bronchodilation in patients with COPD who otherwise respond to β₂-agonists and/or anticholinergic drugs. These results suggest that the change in lung function, seen during long-term dosing with cilomilast, is not the result of maintenance of acute bronchodilation.

This is the first study examining acute bronchodilation following the use of the PDE 4 inhibitor cilomilast and the combined use of cilomilast with inhaled bronchodilators in patients with COPD. The results of the present study show that a single dose of cilomilast does not produce acute bronchodilation in patients with stable COPD. These results are in keeping with Ukena et al., who demonstrated that a single dose of PDE₃,4 inhibitor zardaverine does not have a significant bronchodilator effect in patients with partially reversible, chronic airflow obstruction [13]. In contrast, such a bronchodilator effect has been observed in patients with moderate asthma using inhaled steroids following a single dose of cilomilast [14]. It does not seem likely that the discrepancy in bronchodilator effect following PDE inhibition between patients with asthma and COPD is due to differences in reversibility of lung function by β₂-agonists, since half the patients with COPD in this study were relatively reversible (>190 ml or >14% from baseline lung function), as were the patients with airflow obstruction in the study by Ukena et al. [13].

A previous study in patients with COPD examining the use of a single dose of theophylline with or without concomitant inhalation of salbutamol (180 μg) and/or ipratropium (36 μg) has shown that the combination of all three medications is superior in improving FEV₁ to theophylline in combination with salbutamol, or ipratropium alone [15]. Furthermore, a small additive effect of salbutamol and ipratropium on top of theophylline has been suggested during 2 weeks of treatment [16,17]. In the present study, a difference in bronchodilating effect between cilomilast in combination with either salbutamol, or ipratropium or both could not be demonstrated, as the study was not powered or designed to examine this outcome.

It is unlikely that selection of patients or methodology biased the results. First, COPD patients for this study were selected using strict criteria. Although some reversibility in lung function following inhalation of salbutamol was allowed, pre-bronchodilator FEV₁/FVC had to be <0.7 and post-bronchodilator FEV₁ <75% of predicted value. This allowed the examination of the bronchodilating effects of cilomilast in COPD patients with a limited reversible component of their lung function. Second, with the currently used design, measurements following 8 h post-dosing with cilomilast were compared to either placebo or cilomilast in combination with inhaled bronchodilators. It would have been ideal if measurements were also performed during the 8 h following inhalation of salbutamol or ipratropium alone. However, due to burden for the patient, this was not added to the study design. Third, lung function measurements were performed at hourly intervals. Analysis of plasma samples for cilomilast showed that, as expected, maximal concentrations were reached approximately at 1–4 h after administration of cilomilast. Therefore, it does not seem likely that the maximum effect of cilomilast on lung function was missed.

Cyclic 3', 5'-adenosine monophosphate (cAMP) is a second messenger that mediates airway smooth muscle relaxation and exerts a broad inhibitory effect on the activity of immune and inflammatory cells [8]. By blocking the cAMP-degrading enzyme PDE₄, PDE₄ inhibitors including cilomilast affect the intracellular concentrations of cAMP, which potentially results in increased airway smooth muscle relaxation and a reduction of airway inflammation. In the present study, maximum plasma concentrations of approximately 1500 ng/ml were observed. Since there was no acute bronchodilation following administration of cilomilast, this may suggest that the basal levels of cAMP were insufficient to result in cause relaxation of smooth muscle in this COPD population. It is known that phosphodiesterase inhibitors do not increase intracellular cAMP levels per se but exert...
an effect in the maintenance of levels by inhibiting degradation. This further strengthens the argument that in those patients responsive to inhaled salbutamol an additive or synergistic effect could be envisaged [18].

During continued treatment of 6 weeks with cilomilast, 15 mg bid, lung function improves in patients with COPD [9]. Together with the present finding that a single dose of cilomilast does not result in bronchodilation, this may suggest that prolonged treatment with cilomilast affects airway inflammation rather than smooth muscle tone, and thereby lung function in patients with moderate COPD. Whether chronic cilomilast use reduces airway inflammation in COPD and whether it affects the prognosis of COPD needs to be further evaluated.

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References


