Summary

✓ Roflumilast is an inhibitor of phosphodiesterase-IV (PDE4), a cellular enzyme that is linked to airway inflammation in asthma and chronic obstructive pulmonary disease (COPD).

✓ In clinical trials, roflumilast produced significant improvements in FEV₁ (forced expiratory volume in one second) and PEF (peak expiratory flow) compared with low-dose inhaled beclomethasone in asthma patients, and compared with placebo in COPD patients. Roflumilast reduced the use of rescue medication in both populations. COPD patients on roflumilast experienced fewer exacerbations.

✓ The most common adverse effects reported in roflumilast trials were diarrhea, nausea, headache, and abdominal pain.

✓ Evidence is only available in non-peer-reviewed format abstracts. Most of the measures used are markers of clinical effects as opposed to clinical outcomes. More studies are needed to determine the role of roflumilast in the treatment of asthma and COPD.

The Technology

Roflumilast is a selective inhibitor of PDE4 for oral use. PDE4 is the main type of phosphodiesterase located in airway structural and inflammatory cells. The inhibition of PDE4 suppresses the inflammatory activity in many airway cells that are implicated in the pathogenesis of asthma and COPD, and that contribute to the clinical manifestations.

Regulatory Status

Roflumilast (Daxas™, ALTANA Pharma Inc.) has not been approved for use in Canada. In the US, ALTANA has delayed its application to the Food and Drug Administration (FDA) because of ongoing phase III trials. Regulatory approval for roflumilast (ALTANA Pharma AG, Germany) is pending in Europe after submission to the European Medicines Agency in February 2004.

Patient Groups

Asthma is a chronic inflammatory disease of the airways. It is characterized by intermittent or persistent symptoms including shortness of breath (dyspnea), chest tightness, sputum production, wheezing, and coughing. In the last 20 years, asthma has become increasingly prevalent in young children. It affects an estimated 2.5 million Canadians (12% of children and 8% of adults).

COPD is a progressive, partially reversible respiratory disease that typically occurs in older patients with a history of smoking. Patients with COPD may present with increased sputum production (bronchitis), chronic airflow obstruction, impaired gas exchange (emphysema), and cardiovascular and other systemic changes. Acute exacerbations of COPD are a frequent cause of morbidity and contribute to mortality. An estimated 3.7% of Canadians who are older than 35 years have probable COPD. In 1999, COPD was the fourth leading cause of death among men and the fifth among women.
Current Practice

Drugs that are used in the outpatient treatment of asthma are categorized as relievers or controllers.\(^8\) Relievers, which have bronchodilating effects, are used to treat acute symptoms. They are best represented by the short-acting beta-2 agonists (SABAs) for inhalation. Controllers have anti-inflammatory effects. Inhaled corticosteroids (ICS) are the controller of choice and are indicated in all but the mildest cases of asthma. When the use of one drug cannot ensure adequate symptom control, there is evidence supporting the use of a long-acting beta-2 agonist (LABA) in addition to an ICS.\(^8\)

Other add-on therapies include leukotriene receptor antagonists, methylxanthines (e.g., theophylline), and infrequently, cromoglycate and nedocromil.\(^8\)

Bronchodilators (beta-2 agonists, anticholinergics, and methylxanthines) form the mainstay of COPD treatment.\(^11\) The first-line treatment for regularly symptomatic patients is the combination of an inhaled short-acting anticholinergic (ipratropium) and a SABA as needed. If a SABA is regularly used more than twice a day, a long-acting bronchodilator for inhalation, such as a LABA or tiotropium, should be considered.\(^11\) ICS are not recommended as first-line therapy in COPD, but may be used in moderate to severe disease to reduce the frequency of exacerbations.\(^11\) Paramount in the management of COPD is smoking cessation, the only intervention that is known to slow the progression of the disease.\(^11\)

The Evidence

Asthma

One double-blind, double-dummy, parallel group study compared daily roflumilast 500 µg with low-dose (200 µg twice daily), inhaled beclomethasone dipropionate (BDP). The 12-week study involved 499 symptomatic asthma patients. Both roflumilast and BDP produced significant (\(p<0.001\)) improvements in FEV\(_1\), FVC (forced vital capacity), and morning PEF versus baseline.\(^13\) Both treatments also significantly (\(p\leq 0.001\)) reduced asthma symptom scores and the use of rescue medication.\(^13\) Roflumilast produced less favourable results on all outcome measures compared with BDP, although the differences between treatments were not statistically significant.\(^13\)

COPD

A double-blind, randomized controlled trial was conducted in 516 patients with moderate to severe COPD during a 26-week period. At baseline, patients were randomized to receive daily placebo (n=172), 250 µg roflumilast (n=175), or 500 µg roflumilast (n=169). Results showed statistically significant improvements in FEV\(_1\) (\(p<0.001\)) and morning PEF (\(p<0.012\)) when roflumilast was compared with placebo.\(^14\)

<p>| Table 1: Outcome measures from RECORD study(^{15,16}) |
|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th><strong>Placebo</strong></th>
<th><strong>Roflumilast 250 µg</strong></th>
<th><strong>Roflumilast 500 µg</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients (n)</td>
<td>280</td>
<td>576</td>
</tr>
<tr>
<td>Change in FEV(_1) (mL)(^*)</td>
<td>NR</td>
<td>74±18 (39, 108) †</td>
</tr>
<tr>
<td>Change in FVC (mL)(^*)</td>
<td>NR</td>
<td>71±31 (12, 131) †</td>
</tr>
<tr>
<td>Patients with an exacerbation,(^‡) n (%)</td>
<td>98 (35)</td>
<td>207 (36)</td>
</tr>
<tr>
<td>Mean exacerbations per patient(^§)</td>
<td>1.13(^‡) (^\alpha)</td>
<td>1.03(^‡) (^\alpha)</td>
</tr>
<tr>
<td>SGRQ total score(^§)</td>
<td>-1.71(^‡) (^\alpha)</td>
<td>-3.35(^‡) (^\alpha)</td>
</tr>
</tbody>
</table>

FEV\(_1\)=forced expiratory volume in one second, FVC=forced vital capacity, NR=not reported, SGRQ=St. George’s Respiratory Questionnaire

\(^*\)Changes in FEV\(_1\) and FVC are reported as least squares mean increases versus placebo: LSMean±Std Err
Mean (95% CI); \(^\alpha\) \(p<0.0001\), \(^\beta\) \(p=0.0193\), \(^\gamma\) \(p=0.0002\) for change versus placebo; \(^\delta\) all exacerbations: mild, moderate, and severe; \(^\epsilon\) \(p=0.0029\), \(^\zeta\) \(p<0.025\), \(^\eta\) \(p<0.0001\) for change versus baseline.
The Canadian Coordinating Office for Health Technology Assessment (CCOHTA) is funded by Canadian federal, provincial and territorial governments. (www.ccohta.ca)

The exacerbation rate per patient was lower in the 500 µg roflumilast group versus the placebo group (0.09 exacerbations per patient versus 0.15 exacerbations per patient respectively). The statistical significance was unreported.

The RECORD study, a double-blind randomized controlled trial, compared roflumilast with placebo in 1,411 patients with moderate to severe COPD. After 24 weeks of treatment, roflumilast produced significant dose-dependent improvements in FEV1 and FVC compared with placebo. 500 µg roflumilast daily significantly reduced the number of patients experiencing an exacerbation (relative risk: 0.80; 95% CI: 0.65, 0.98; number needed to treat: 14; 95% CI: 7, 335) and the average number of exacerbations per patient (Table 1).

This effect was mainly based on a reduction in mild exacerbations; neither dose of roflumilast significantly reduced moderate or severe exacerbations. The health-related quality of life was evaluated using the St. George's Respiratory Questionnaire (SGRQ). Roflumilast improved quality of life to a greater degree than placebo (Table 1). None of the treatment groups reached the minimal criteria for clinical improvement (i.e., -4.0 units).

Adverse Effects

Limited data from available roflumilast trials suggest that the drug is well tolerated in most patients. As PDE4 is located in a variety of inflammatory cells, PDE4 inhibitors are being investigated for the management of inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis, osteoporosis, allergic rhinitis, and skin diseases. As PDE4 is located in a variety of inflammatory cells, PDE4 inhibitors are being investigated for the management of inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis, osteoporosis, allergic rhinitis, and skin diseases. As PDE4 is located in a variety of inflammatory cells, PDE4 inhibitors are being investigated for the management of inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis, osteoporosis, allergic rhinitis, and skin diseases. As PDE4 is located in a variety of inflammatory cells, PDE4 inhibitors are being investigated for the management of inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis, osteoporosis, allergic rhinitis, and skin diseases.

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Implementation Issues

The findings from clinical trials are based on the markers of clinical effects. There is a need to better evaluate how roflumilast compares with existing therapies for asthma and COPD in terms of clinical benefits (patients’ functional capacity, emergency visits, hospitalization, mortality) and the potential for harm. Long-term safety data are also lacking. From clinical practice and policy-making perspectives, it would be important to determine whether specific populations of asthma and COPD patients would benefit from roflumilast or would be more at risk for adverse events.

References


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