Early data about the use of roflumilast in patients with COPD

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ABSTRACT: Roflumilast is a new second line anti-inflammatory drug, approved by the FDA in March 2011, for the treatment of patients with a specific phenotype of Chronic Obstructive Pulmonary Disease (COPD). In this review article, after systematically reviewing the latest published references on roflumilast, we aim at presenting the experimental and clinical results that have emerged so far, concerning the benefits and the limitations of its use and the future prospects for the optimization of its effects.

Key Words: roflumilast, COPD, chronic bronchitis, exacerbation, anti-inflammatory

1. INTRODUCTION

COPD is characterized by the progressive worsening and irreversible limitation of the expiratory airflow, primarily as a result of the chronic inflammation of the distal branches of the tracheobronchial tree. It is classified, according to GOLD (The Global Initiative for Chronic Obstructive Lung Disease) in four stages, based on spirometric results pre- and post- bronchodilation (Table 1). Its prevalence is rather underestimated, while this nosologic entity is directly associated with high morbidity and mortality. COPD is estimated to be the third leading cause of deaths worldwide, constituting a significant financial burden to the modern, long-suffering from crisis economy. COPD exacerbations, mainly reported in winter, are directly correlated with adverse prognosis

Modern therapeutic strategy of COPD involves two classes of drugs: bronchodilators and anti-inflammatory drugs (Table 2). New pharmaceutical agents are under development, while roflumilast, a selective inhibitor of the enzyme phosphodiesterase 4(PDE4) – first prepared in 1993- has already been approved by the FDA for its introduction in clinical practice, having however indication for a specific phenotype of COPD². Practically, roflumilast is the first non-steroidal anti-inflammatory agent introduced in clinical practice as a second-line drug for the therapeutic management of patients suffering from COPD³.

Table 1. GOLD COPD classification

<table>
<thead>
<tr>
<th>Stage I (Mild)</th>
<th>Stage II (Moderate)</th>
<th>Stage III (Severe)</th>
<th>Stage IV (Very severe)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁/FVC&lt;0.7</td>
<td>FEV₁/FVC&lt;0.7</td>
<td>FEV₁/FVC&lt;0.7</td>
<td>FEV₁/FVC&lt;0.7</td>
</tr>
<tr>
<td>FEV₁ ≥ 80% predicted</td>
<td>FEV₁ 50-79% predicted</td>
<td>FEV₁ 30-49% predicted</td>
<td>FEV₁ &lt;30% predicted, or</td>
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<td></td>
<td></td>
<td></td>
<td>&lt;50% predicted with chronic respiratory failure present</td>
</tr>
</tbody>
</table>

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Its inhibitory effect on PDE4 induces the intracellular accumulation of cyclic adenosine monophosphate (cAMP). Subsequently, protein kinase A (PKA) is activated. In a randomized clinical study conducted by Hohfeld et al.\(^4\) it was found that roflumilast blocks the recruitment of neutrophils and eosinophils. Roflumilast also inhibits the secretion of cytokines (especially TNF-α), but it lacks bronchodilator properties. The exact mechanism of its action is still under investigation. It is administered at a daily dose of 500 μg per os and it is rapidly metabolized in roflumilast-N-oxide (>90% of total activity) by the enzymes of cytochrome P450, especially 3A4 and 1A2. Thus, the co-administration with drugs that induce cytochrome’s enzymes is contraindicated (for example: rifampicin 600 mg, fluvoxamine 50 mg). After oral administration, roflumilast is quickly and completely absorbed (maximum plasma concentration in one hour), while its bioavailability is estimated at almost 80%\(^5\)\^-\(^7\).

After systematically reviewing 11 recent relevant publications (table 3), we aim through this review article at presenting the early data from the use of roflumilast in clinical practice and the nomination of future prospects for its position in modern therapeutic patterns in COPD, as well.

### 2. EXPERIMENTAL DATA

Experimental studies have shown in vitro that roflumilast and its main metabolite, roflumilast-N-oxide reduce LPS (lipopolysaccharide) –endotoxin induced secretion of TNF-and chemokines that contribute to the recruitment of monocytes and T-lymphocytes, such as CCL2, CCL3, CCL4, CXCL9, and CXCL10\(^8\). Nonetheless, equivalent suppressive effect on the secretion of chemokines that mobilize neutrophils, such as CXCL1, CXCL5 and CXCL8, was not proved. Therefore, roflumilast exerts a suppressant effect on two of the three major cellular populations, which are involved in the pathophysiology of COPD\(^9\).

At a molecular level, roflumilast induces: a) increased expression of HDAC2 (histone deacetylase 2) and MKP1 (mitogen-activated protein kinase phosphatase 1), b) inhibition of kinases p38, JUN, ERK1/2 and finally c) expression of NF-κΒ (nuclear factor kappa-light-chain-enhancer of activated B cells), modifying the subject oxidative stress.

Based on this effect of roflumilast, it is possible that, if it is added to a therapeutic pattern including inhaled corticosteroids (ICs), it is feasible to reverse the resistance to them, and thus optimize the anti-inflammatory result\(^10\)\^-\(^12\).

Additionally, there is experimental evidence that roflumilast exerts a stimulatory effect on VEGF (Vascular Endothelial Growth Factor), which contributes to the growth and survival of endothelial cells, as well as to the maintenance of the vascular tone in the pulmonary microcirculation\(^13\).

### 3. CLINICAL DATA

Based on clinical trials and meta-analyses conducted until now, there is consensus as to the phenotype of those patients with COPD, who would benefit from daily administration of roflumilast, as a second-line drug: COPD stage III-IV, with chronic bronchitis and frequent exacerbations (some authors suggest >2 exacerbations/year and others >4)\(^14\)\^-\(^15\). It should be noted, that roflumilast induced decrease in the exacerbation rate is underestimated, when it is added on a regimen consisting of first-line drugs\(^16\).

Martinez et al. conducted a one year double-blind...
multicenter study on 1945 selected patients. Nine hundred and seventy-three of them were given roflumilast (group A) and 972 received placebo (group B). It was shown that in group A there was a reduction in yearly exacerbations by almost 14%, compared to group B. However, twice as many patients of group A, discontinued treatment due to roflumilast’s side effects\(^\text{17}\).

Yan et al. after a meta-analysis of eleven different clinical trials conducted on 9675 patients, selected with common criteria, concluded that roflumilast: a) reduces the mean rate of annual exacerbations (p<0.00001), b) improves FEV\(_1\) (p<0.00001) and c) does not affect the quality of life and the mortality rate of these patients (p=0.49 and 0.56 respectively)\(^\text{18}\). Oba et al. conducted a respective meta-analysis of eight clinical trials in a total of 8698 patients with the typical phenotype and reached similar conclusions\(^\text{19}\).

Wedzicha et al. substantiated that roflumilast reduces the number of exacerbations per year (p=0.0148) and stabilizes the severity of the disease (p=0.0018)\(^\text{20}\). Regarding to the spirometric profile of these patients, Pinner et al. proved that roflumilast increases FEV\(_1\) by 36-88 mL (comparison of patients with the same phenotype, half of whom received roflumilast and the other half received placebo), noting however that a high percentage of these patients (9-16%) dropped out of therapy with roflumilast within the first twelve weeks, due to intolerable side effects. They also assess that roflumilast does not affect the quality of life of the patients with the typical phenotype\(^\text{21}\).

After systematic evaluation and processing of 29 randomized, placebo-controlled clinical trials, conducted on a total of 19111 patients, with COPD stage II-IV and an average age of sixty four years old, Chong et al.

<table>
<thead>
<tr>
<th>Researchers</th>
<th>Results</th>
</tr>
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| Martinez et al.\(^\text{17}\) | * 13.7% ↓ of exacerbations  
* 2x patients treated with ro.(in comparison with those given placebo) withdrew from therapy |
| Yan et al. \(^\text{18}\)     | * ↓ mean exacerbation rate  
* ↑ FEV\(_1\)  
* quality of life |
| Oba et al. \(^\text{19}\)     | * ↓ mean exacerbation rate  
* ↑ FEV\(_1\)  
* ↔ quality of life  
* ↑ withdrawal from therapy due to side effects |
| Wedzicha et al. \(^\text{20}\) | * ↓ mean exacerbation rate  
* Stabilizes clinical condition |
| Pinner et al. \(^\text{21}\)  | * ↑ FEV\(_1\)  
* ↑ withdrawal from therapy due to side effects |
| Chong et al. \(^\text{22}\)   | * ↑ FEV\(_1\)  
* ↓ mean exacerbation rate  
* ↔ quality of life  
* ↔ exercise tolerance |
| Lei Pan et al. \(^\text{23}\) | * ↑ effectiveness of LAMAs  
* ↓ dyspnea |
| Mills et al. \(^\text{24}\)   | * ↑ effectiveness of LAMAs |
| Giembycz et al. \(^\text{25}\) | * Synergy with LABAs  
* ↑ effectiveness of ICs |
| White et al. \(^\text{26}\)   | * Controversy about its effect on MACEs |
| Lone et al. \(^\text{27}\)    | |

**Abbreviations:** FEV\(_1\), Forced Expiratory Volume in 1”; LAMAs, long-acting muscarinic antagonists; LABAs, long-acting beta-2 agonists; ICs, inhaled corticosteroids; MACEs, major adverse cardiovascular events.
demonstrated the following regarding to roflumilast and cilomilast: a) these agents increase FEV\textsubscript{1} by 45.6 mL, b) they practically do not improve the quality of life and the symptoms of these patients, c) they do not alter patients’ exercise tolerance and d) they reduce the mean exacerbation rate, preventing more aggressive clinical intervention\textsuperscript{22}.

Lei Pan et al. noted that roflumilast may have a favorable impact on dyspnea of patients with the above phenotype, while it appears that co-administration of roflumilast with anticholinergic agents is superior to monotherapy\textsuperscript{23}, reinforcing the aspect of Mills et al., expressed already in 2011, that roflumilast in co-administration with LAMAs (Long Acting Muscarinic Antagonists) provides clear benefits to patients with chronic bronchitis and at least two exacerbations per year\textsuperscript{24}.

Furthermore, roflumilast appears to act in synergy with LABAs (Long Acting \textsubscript{B}_{2}-Agonists), enhancing that way the anti-inflammatory action of ICs (Inhaled Corticosteroids)\textsuperscript{25}. The potential cardiovascular benefit of roflumilast in patients with COPD is under investigation. There is evidence that it may contribute to the decrease of the incidence of cerebrovascular events\textsuperscript{26}, but not that of the other major adverse cardiovascular events (MACEs). Concerns about the higher incidence of atrial fibrillation and atrial multifocal tachycardia in COPD patients compared to those that received placebo are on the rise as well\textsuperscript{27}.

It seems that roflumilast is a reliable second-line agent, possibly cost-effective\textsuperscript{28}, as an add-on treatment to the first-line bronchodilator and anti-inflammatory drugs, for those COPD patients with well-defined phenotypic traits.

A summary of the results of the above clinical studies is shown in table 3.

4. RESTRICTIONS IN ADMINISTRATION

In all clinical trials and studies at present there is a consensus regarding the indications of roflumilast’s administration as well as its adverse effects, which constitute a significant obstacle in its clinical use as an add-on treatment. These side effects concern mainly the gastrointestinal tract (nausea, vomiting, weight loss, and diarrhea) and the Central Nervous System (headache, insomnia, drowsiness). The average weight loss amounts to 2.1 kilograms. Most of them occur within the first 4-12 weeks after the start of administration, leading to a high percentage of withdrawal from treatment (9-16\%)\textsuperscript{14-15,19}.

We should especially mention the higher incidence of atrial fibrillation and suicidal ideation in patients who received roflumilast, compared to those that received placebo (0.4 and 0.08\% of patients with COPD versus 0.2 and 0\%, respectively\textsuperscript{19}). Therefore, roflumilast is contraindicated in patients suffering from depression and having expressed suicidal thoughts at least once before\textsuperscript{7}.

Absolutely contraindicated is the administration to patients with chronic and advanced liver disease (Child-Pugh Stages B-C), while no dose adjustment is required in patients with renal impairment\textsuperscript{9,29}.

As it has been previously said, the co-administration with drugs that induce P450 cytochrome’s enzymes is also contraindicated\textsuperscript{30}.

5. FUTURE PROSPECTS-CONCLUSIONS

It appears that the mechanism of nausea and emesis is induced by the inhibition of the subtype D of PDE4 (PDE4D), while the anti-inflammatory effect is mediated via the inhibition of the subtype B (PDE4B). Hence, a more selective inhibitor of the second isoenzyme could possibly optimize the needed action, being at the same time better tolerated\textsuperscript{7,10}.

RPL554, a combined conjugated PDE3/PDE4 inhibitor is under investigation. It exerts both bronchodilatory (PDE3 inhibition) and anti-inflammatory (PDE4 inhibition) effects, while it can be administered via inhalation, minimizing that way its systematic absorption, and thus the occurrence of intolerable adverse events\textsuperscript{11-13}. There are also new signs, that such an agent transcends a simple PDE4 inhibitor, because it is able to enhance and prolong the effects of LABAs and ICs\textsuperscript{31}.

In conclusion, roflumilast is a second-line agent, indicated for patients suffering from COPD and with a specific phenotype: chronic bronchitis and at least 2 exacerbations per year. This new drug needs further evaluation, through experimental and clinical studies, in order to better evaluate its clinical utility.

6. CONFLICT OF INTEREST

The authors would like to state no conflict of interest.
Νεότερα δεδομένα για τη χρήση της ροφλουμιλάστη στη Χρόνια Αποφρακτική Πνευμονοπάθεια: άρθρο σύντομης ανασκόπησης
Πατουλιάς Δημήτριος 1, Καλογήρου Μαρία Στυλιανή 1, Παπακωνσταντίνου Ελένη 2

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2Καθηγήτρια, Β’ Εργαστήριο Φαρμακολογίας, Τμήμα Ιατρικής, Σχολή Επιστημών Υγείας Α.Π.Θ.

Περίληψη: Η ροφλουμιλάστη αποτελεί έναν νεότερο αντιφλεγμονώδη παράγοντα 2ης γραμμής για τη θεραπεία ασθενών με συγκεκριμένο φαινότυπο Χρόνιας Αποφρακτικής Πνευμονοπάθειας. Στο παρόν άρθρο μετά από αναδίφηση της πλέον πρόσφατης διεθνούς βιβλιογραφίας, επιχειρείται η παρουσίαση των έως τώρα πειραματικών και κλινικών αποτελεσμάτων, όσον αφορά στα οφέλη που προκύπτουν από τη χρήση της, τους περιορισμούς της χορήγησής της, αλλά και τις μελλοντικές προοπτικές για τη βελτιστοποίηση της δράσης της.

Αξίων Κλειδιά: ροφλουμιλάστη, ΧΑΠ, χρόνια βρογχίτιδα, έξαρση, αντιφλεγμονώδης

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