Review Article

Roflumilast: First approved oral selective PDE4 inhibitor for the treatment of COPD

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Abstract

Roflumilast is a first-in-class oral selective anti-inflammatory drug which is a PDE4 inhibitor. It has been approved by regulatory authorities in the Europe and US in 2010 and 2011 respectively for the prevention of acute exacerbations among patients with severe COPD. Since then, the drug has been studies in different populations in clinical trials as well as real world studies. The studies looked at different end points such as the quality of life, improvement in spirometry indices as well as the ability of the drug to prevent exacerbations and hospital admissions. There was a variable response seen in these studies. This article seeks to review the evidence for the role of roflumilast in COPD from these recent studies since its approval.

Keywords: Roflumilast, Exacerbation, Anti-Inflammatory, Phosphodiesterase, COPD

Introduction

Chronic obstructive pulmonary disease is currently the third leading cause of death globally and is purported to become the most common cause of death within the next decade. [1]Smoking is the principal risk factor of COPD [2]. Bronchodilators and anti-inflammatory agents are currently used in the pharmacologic management of COPD. Bronchodilators such as beta agonists and muscarinic antagonists are useful for symptom relief but may not have many roles in preventing the progression of disease[3]. Inhaled corticosteroids are useful in preventing exacerbations and have also shown to improve the quality of life in COPD. However, they do not improve mortality or lung function even with long term usage[4]. Methylxanthines may be an alternative option in these patients but have limited efficacy[5]. Thus, COPD does appear to be a condition that requires better drugs which offer more than what the current battery of drugs offers.

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Roflumilast is a first-in-class molecule, a phosphodiesterase-4 (PDE-4) inhibitor that was approved by the US FDA for the management of COPD. This article attempts to review the evidence from the literature on its efficacy, safety, and the current status of the molecule in the management of COPD.

Mechanism

Phosphodiesterases (PDE)is a large enzyme family whichis subdivided into eleven (PDE_1 –PDE_{11}) different isoforms [6].Inhibition of phosphodiesterase will increase cyclic guanosine monophosphate (cGMP) and cyclic adenosine monophosphate (cAMP) which act intra-cellularly for anti-inflammatory action [7]. Second messenger (cAMP) will act on airway smooth muscle and lead to inhibition of inflammatory mediators [8]. PDE4 inhibitors will affect the action of immune agents and prevent neutrophil inflammation and act through various pathways for anti-inflammation action [9].Roflumilastis a PDE-4inhibitor which inhibits the breakdown of cAMP into adenosine monophosphate(AMP). This results inthe accumulation of intracellular cAMP [10]. PDE-4 inhibitors with ICS will reducecytokinerelease and increase the anti-inflammatory effect in CD8+ cells [11]. Roflumilast decreases the pulmonary inflammation of the lungs by

reducing the prolylendopeptidase and acetyl-proline-glycine-proline level in sputum [12].Roflumilast reduces inflammation in the airway by inhibiting endotoxin-induced various macrophages such as eosinophil, neutrophil, and improve lung function. [13]

Pharmacokinetics

After administeringa single oral dose of roflumilast, absorption is quick with the bioavailability of 80% (approximately) and its metabolism occurs through the liver [7].Roflumilast reaches peak concentration in plasma within one hour and is highly bound to proteins in plasma[14].Food does not inhibit roflumilast activity but it will delay T_{max} by 0.9 hrs and reduce C_{max} by 20% [15]. In patients, compared with various doses of roflumilastadministered, 500µg of roflumilast was found to improve $FEV_1$of patients [16].

Pharmacokinetics of roflumilast 500µg on concomitant administration with 10mg montelukast in steady conditionsremains unchanged [17].

Efficacy

Since its regulatory approval,roflumilast has been evaluated in several clinical trials and real-world studies. In a study by Criner et al, 64 patients having moderate to severe COPD were randomized to receive roflumilast or placebo. It was observed, that therewas no difference in the time for first readmission or death between the two groups. There was no difference in the quality of life, as assessed by St. George's Respiratory Questionnaire. There were no differences in the total number of re-hospitalizations in either group [18].

DINO and DACOTA were two prospective observational studies that were performed in patients with severe to very severe COPD, to receive new treatment with roflumilast 500µg once daily. These studies were carried out in the German population. Randomized controlled trials have a limitation of not being representative of daily practice. For instance, there is a greater than average treatment adherence in RCTs than clinical practice. There is also an unsurprisingly greater predilection to use surrogate endpoints than hard endpoints in clinical trials. It has been argued, that the quality of life, is a better indicator of the patient's perception and experience with respect to a particular drug therapy. In this context, the DINO and DACATO studies chose to evaluate principally the quality of life in users of roflumilast. Change in clinical COPD questionnaire total score, from the baseline, following roflumilast intake was considered the primary end point. The minimal clinically important difference for the above end point was fixed at 0.41. Secondary endpointsincluded changes in CCQ (Clinical COPD questionnaire) domain scores, COPD Assessment Test (CAT) and, Post Bronchodilator FEV_1. Approximately 9000 patients were included in the two studies. Treatment with roflumilastshowed an improvement in the CCQ total and domain scores greater than the prefixed MCID (minimal clinically important difference). There was also a significant improvement in the CAD score at 6 months. Patients with frequent exacerbation had a greater benefit with roflumilast than those with non-frequent exacerbation. There was also a much greater improvement in the post-bronchodilator FEV_1in the DACOTA study, than what was earlier observed in RCTs (200ml over 6 month vs 50ml over a year). More than one-third of participants in both the studies discontinued therapy with roflumilast. This is consistent with that seen in earlier RCTs [19].In a study by Martinez et al, conducted in patients with severe to very severe COPD with a history of two or more exacerbations or hospitalized in the preceding year, roflumilast was evaluated for its effect on the frequency of exacerbations. All these patients continued to receive inhaled corticosteroids/ LABA with or without LAMA within 3 or 4 months. Patients (n=2354) were randomised to receive either roflumilast 500µg once daily or placebo in a 1:1 ratio for 52 weeks in a double-blind manner. At the end of 1 year, it was noted that roflumilast did not have any substantial effect in preventing exacerbation in comparison with placebo. Only patients with a history of more than 3 exacerbations and or one or more prior hospitalization showed a reduction in the rate of exacerbation. The discontinuation rate with roflumilast was almost double that seen with placebo (11.7 vs 5.4). These findings are not in agreement with the earlier (REACT Study). In the REACT study, there was a significant reduction in the rate of severe and moderate exacerbation when compared to placebo. One major difference between the (RE^2SPOND Study) and REACT Study, was the higher number of patients having past history of repeated exacerbation.(25 vs 11 %).Thus roflumilast appears to be ideally suited for those patients with moderate to severe exacerbations and those with past history of more than three exacerbations [20].

Lee et al undertook a double blind randomized control trial in Korean patients with COPD. A total of 207 participants were randomized to receive roflumilast or placebo. At the end of 12 weeks, there was an increase in the least square means of the post-bronchodilator FEV_1 by 43ml and it reduced by 60ml among users of placebo (p=0.001). However, patients-centric outcomes including quality of life, exercise, and dyspnoea were not evaluated. The low sample size and lack of female participants in the study hampered the generalizability of these findings. [21]

In a study by Liu et al,roflumilast was evaluated in Chinese patients with COPD for atleast 12 months,who also had a history of being clinically stable for atleast one month before the study. Patients were randomized to receive roflumilast or placebo. FVC, FEV_1, $FEF_{25-75\%}$ showed improvement in the roflumilast in comparison with placebo at the end of 12 months and as well as 3 months after stopping the treatment. There was also a lowering of the total SGRQ score in the roflumilast group in comparison with the placebo. This trial was fraught with certain limitations such as being a single centre and restricted to the Chinese Han ethnicity. [22]

Safety

In real-world study, alow percentage of discontinuation occurred during treatment due to adverse events,among patients with COPD receiving 250µg of roflumilast than500µg of roflumilast. [23]Common adverse effects include anorexia, nausea, headache,and weight loss. No life-threatening adverse effectswere reported [23,24]. However, there is a risk of suicidal ideation and behaviour based on post-marketing reports and one should exercise prudence in prescribing drugs in patients with depression or other risk factors for suicide. [25]

Table 1:Some Important studies which based on Roflumilast

Corresponding Author	Year	Sample Size	Country	Duration	Interventional Group	Control Group	Result
Sang-Do Lee [21]	2015	260	Korea	12 weeks	Roflumilast (500 µg)	Placebo	Among Korean patients with moderate to severe COPD, lung activity was found to have improved significantly in spirometry. End points like pre/post bronchodilator FEV, FVC,peak expiratory flow on roflumilast group with no tolerability issue was raised.
Martinez [29]	2016	1178	U S	52 weeks	Roflumilast (500 µg)	Placebo	Roflumilastwas found to improvethe lung activity and decreasedexacerbation in individuals with history of hospitalizationwhich was not statistically significant (CI:0.8-1.04, P= 0.163)
Hakan-Gunen [30]	2019	83	Turkey	18 months	Roflumilast 500µg	Nil	Decreased COPDexacerbation (P<0.001) and hospitalization (P<0.001) was reported in patients receivingroflumilast compared to earlier treatment.
Dan Peng [31]	2018	120	China	12 months	Roflumilast 500µg	Placebo	In this real world study, after three and twelve month of follow-up, lung activity was improved and FEV, FEF, FVC was considerably better from the baseline value,roflumilast at 5mg/kg significantly decreased post-PAE microvascular hyperpermeability (P < 0.05) compared with control.Also, SGRQ scale, quality of life among roflumilast group was found to be improved.

Current status

Roflumilast has been approved by FDA in 2011 and approved by European Medicines Agency on April 2010 for the treatment of severe COPD with chronic bronchitis [26]. In India, 2014,CDSCO approved roflumilast for the maintenance management of COPD associated with bronchitis[27]. In India,the estimated price of one strip (10 Tab) of roflumilast isaround Rs 125/-[28]. There are seven on-going trials based on roflumilastwhich are currently recruiting patients in various indications such as chronic bronchitis,asthma,obesity,lymphoma, bronchiectasis, and chronic plaque psoriasis [32].

Conclusion

Roflumilastis an oral drug approved for preventing exacerbations in severe COPD that are associated with chronic bronchitis and who have a history of frequent exacerbations. This could be a valuable alternative when patients do not respond to the combination of LABA and LAMA. The high discontinuation rate in trials does not give much confidence for prescribers to choose this molecule. However, it remains to be seen if roflumilast could in future replace the first-line drugs for the management of the earlier stages of the disease.

Abbreviation

REACT-Roflumilast and Exacerbations in Patients Receiving Appropriate Combination Therapy
FDA-Food and drug administration
CDSCO-Central Drugs Standard Control Organisation
ICS-Inhaled corticosteroid
AE- Adverse event
cAMP-Cyclic adenosine monophosphophate

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