

Roflumilast: a green signal is yet to come

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Chronic obstructive pulmonary disease (COPD) is a disabling disease and prevalent across nations with a huge economic impact. COPD is the third leading cause of death in the United States and will become the third leading cause of death worldwide by 2030. The increasing morbidity and mortality of COPD are a major threat to public health (1,2). Epidemiological evidence has shown that a substantial proportion of COPD mortality and morbidity is related to cardiovascular disease (3-5). Multiple studies have demonstrated that systemic inflammation and release of inflammatory mediators in COPD may potentially mediate its cardiovascular complications (6). Others have suggested shared risk factors such as smoking, advanced age, physical inactivity and treatment related side effects increase susceptibility to concomitant cardiovascular disease in COPD (7-9). Despite major advances in pharmaceutical research, the data is lacking on cardiovascular safety of COPD medications. Recently, US Food and Drug Administration (FDA) has approved roflumilast—a new selective phosphodiesterase (PDE)-4 inhibitor that targets proinflammatory mediators involved in the pathogenesis and exacerbations of COPD. Contrary to theophylline, a non-specific PDE inhibitor, the principal action of roflumilast is to inhibit isoenzyme subtype PDE4 which is highly specific and expressed in airway inflammatory cells. Inhibition of PDE enzymes increases the intracellular cyclic adenosine monophosphate (cAMP) and exerts an inhibitory effect on various inflammatory and immunomodulatory cells involved in the pathogenesis of COPD. Roflumilast, a selective PDE4 inhibitor, is given orally, once daily for the maintenance treatment of COPD patients with chronic bronchitis and at risk of

exacerbations (10,11).

White and colleagues reported the results of cardiovascular safety of roflumilast in an industry sponsored, pooled analysis of 14 placebo-controlled trials in COPD patients (12). The clinical trials that were 12 weeks or longer were included in the pooled analysis. A total of 12,054 patients of which 6,563 patients received roflumilast and 5,491 patients received placebo were retrospectively analyzed for adjudicated diagnosis of a major adverse cardiovascular event (MACE) endpoint. The authors reported significantly fewer MACE events with roflumilast as compared to placebo (hazard ratio =0.65, 95% confidence interval of 0.45 to 0.93, $P=0.019$). The authors concluded that roflumilast was devoid of a cardiovascular safety signal when treating COPD patients. However caution should be exercised in interpreting these results as the clinical trials included in this analysis were not designed nor powered to detect the difference in cardiovascular outcomes. Secondly, reporting a composite outcome poses a substantive risk of misleading readers by giving them an impression that all components of the composite outcome equally had significant improvement when only one component showed significant improvement and made the composite outcome statistically significant. It may not be appropriate to use the composite outcome if the magnitude of treatment effect is not comparable across the outcome components (13). The incidence of non-fatal stroke was the only component of MACE that showed a statistically significant difference. It may be fair to say that roflumilast could decrease cerebrovascular events but not cardiovascular events or mortality since roflumilast was not associated with lower incidence of such MACE components as compared with placebo.

Thirdly, cardiac arrhythmias were not included in the MACE composite outcome. Various studies have reported the risk of cardiac arrhythmias, especially atrial fibrillation and multifocal atrial tachycardia, which are increased in COPD patients and present a substantial clinical challenge. In our recent meta-analysis, atrial fibrillation (0.4% versus 0.2%; $P=0.02$) was significantly more frequent with roflumilast than with placebo (14). The incidence of atrial fibrillation should have been incorporated in the study.

Fourthly, the study results may not be generalizable since

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many studies included in the COPD safety pool excluded patients with significant cardiopulmonary abnormalities and/or on long-term oxygen therapy. Continuous oxygen therapy and smoking cessation are the only interventions shown to reduce mortality in COPD (15). The cardiovascular safety profile of roflumilast could change when high risk cardiac patients are included in future trials.

Although roflumilast is approved for patients with COPD with severe and very severe airflow limitation and a history of exacerbations, its place in the current armamentarium of COPD treatments and the risk–benefit ratio are still at the center of debate (16). The US Food and Drug Administration (FDA) approved roflumilast in March 2011 for clinical use to reduce the risk of COPD exacerbations, although an advisory panel of outside experts had opposed it by a 5 to 10 vote. The advisory committee felt that a small improvement in lung function did not outweigh its significant side effects, which primarily consisted of gastrointestinal and psychiatric problems, including suicidal behavior, which led to increased withdrawal from clinical studies (17). Roflumilast was finally approved by the FDA after its indication was made more restrictive and a warning about the psychiatric side effects was added to the drug label.

Another PDE4 inhibitor, cilomilast, was rejected by the FDA advisory panel in September 2003, based on concerns over the efficacy of the agent, as well as gastrointestinal side effects. However, the FDA temporarily approved cilomilast in October 2003 but the final approval is contingent on the outcome of additional efficacy and safety studies (18), which are still ongoing. The risk–benefit ratio of the entire class of orally active PDE4 inhibitors appears to be in question and cannot be dismissed. Although White *et al.* tried to prove cardiovascular safety of roflumilast; it will continue to face the test of time because of high dropout rates due to side effects in the clinical trials, unclear risk-benefit ratio, and its questionable cost effectiveness. Our recent systematic review found that although roflumilast did improve lung function, it did not improve the mortality rate or health-related quality of life over placebo. Roflumilast significantly reduced moderate exacerbations but not severe exacerbations (14). Whereas the recent update of COPD guidelines incorporated roflumilast as one of second-line agents (19), the place and role of roflumilast in COPD management are still unclear (20). Post-marketing safety surveillance to further investigate the risk–benefit ratio of roflumilast is warranted before its wider use. The ongoing large randomized trials with the background therapy of an inhaled corticosteroid plus long-acting beta2 agonist would help clinicians to determine the place of roflumilast in the current armamentarium of COPD therapies. (Available from: <http://www.clinicaltrials.gov/ct2/show/NCT01443845?term=roflumilast&rank=12>. <http://www.clinicaltrials.gov/ct2/show/NCT01329029?term=roflumilast&rank=10>). In summary the study by

White *et al.* would not yet give roflumilast a green signal for its preferential inclusion in the care of COPD patients.

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