MINI REVIEW

Chronic obstructive pulmonary disease, its new drug treatments and strategies: A review

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Abstract: COPD is a complicated disease. Current available treatments are just for symptomatic relief and they cannot reverse the damages to lungs tissues due to alveolar destruction in COPD. Research is being conducted to evaluate new treatments and strategies to find specific treatments to minimize the symptoms of COPD. A new mixture of herbal medicine i.e AKL1 has emerged and thought to cure COPD symptoms especially cough related quality of life of COPD patients. Although, the results have showed no significant difference as compared to placebo but researchers recommend further evaluation in a large population (COPD Patients) group. Another medicine Roflumilast, a phosphodiesterase 4 inhibitor, was also found to be effective to treat COPD under specific recommendations with further research needed. Finally another medicine Indacaterol, a novel, once-daily (o.d) inhaled long-acting β2-agonist proved to be effective clinically to treat COPD related broncho-constriction and also increasing the COPD patient’s compliance by reducing the number of doses as compared to other conventional inhaled bronchodilators such as Albuterol.

Keywords: COPD exacerbations, forced expiratory volume, leicester cough questionnaire, St. George's respiratory questionnaire.

INTRODUCTION

COPD, or chronic obstructive pulmonary disease, is a progressive disease that makes it hard to breathe (Siafakas et al., 1995). "Progressive" means the disease gets worse over time. COPD is a collective name for chronic bronchitis and emphysema, two diseases that are almost always caused by smoking. Emphysema is long-term destruction of lungs over time (Viegi et al., 2000) (fig. 1). Bronchitis is inflammation of the inner lining of the Bronchi (fig. 2).

Signs and symptoms

Signs and symptoms of COPD include wheezing, sputum production, shortness of breath, chest tightness, breathlessness, chest infection, cough etc. (Mannino et al., 2007). Many of the symptoms of COPD are similar to those of asthma. Other symptoms of COPD are weight loss, tiredness and ankle swelling. COPD causes include exposure to tobacco smoked in cigars, cigarettes and pipes, passive smoking, air pollution, dust, industrial chemical/toxic fumes and genetic defects such as α1-Antitrypsin deficiency (Seemungal et al., 2001). This deficiency is responsible for increased levels of Elastase that degrades the elastin in lung tissue and results in loss of elastic recoil of alveoli. Some complications of COPD are pulmonary hypertension (pulmonary vessel constriction due to alveolar hypoxia & acidosis), pneumonia, acute respiratory failure, lung cancer, heart problem, depression. Difference between COPD and asthma is that in COPD there is a permanent damage to the airways (Leidy et al., 2015). The narrowed airways are fixed, and so symptoms are chronic (persistent). Treatment to open up the airways is therefore limited. In asthma there is inflammation in the airways which makes the muscles in the airways constrict. This causes the airways to narrow (Kulich et al., 2015). The symptoms are reversible and vary in severity throughout the year. Treatment to reduce inflammation and to open up the airways usually works well (Mullen, 1985; Hunninghake et al, 1983).

Treatment of COPD

As mentioned earlier that COPD causes permanent damage to the lung tissue due to fibrosis and narrowing of the airways and loss of elastic recoil due to alveolar destruction (Zarnouh et al., 2014). For this reason the treatment of COPD is limited and aimed on symptomatic relief as it cannot reverse the damage to lungs.

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**Current treatments**
These are the current treatments that are used for COPD. Bronchodilators e.g. Salmeterol (Long acting beta agonists) and Salbutamol (Short acting beta agonists), Anti-Cholinergics i.e. Ipratropium and Tiotropium, Anti-Muscarinics e.g. Aclidinium, Inhaled steroids and antibiotics. Alpha 1 Anti-Trypsin Deficiency to reduce the elastase burden i.e Tamoxifen (Danazol) or Purified AAT by inhalation or IV-infusion (Trade Name-Prolastin, Aralast).

**Newer drug treatments**
The new drug treatments that have emerged include AKL1, Roflumilast and Indacaterol (Hodge et al., 2014).

**AKL1**
A new patented herbal formulation, AKL1 (AKL International, Ltd, Guernsey, UK), comprising standardized extracts of *Picrorhiza kurroa* (common regional name Asia is kukta), *Ginkgo biloba* (common Urdu name is Pankha plant), and *Zingiber officinale* (common Urdu name is Adrak), has been developed as adjunctive therapy for patients with obstructive lung disease (COPD and asthma) (Grant et al., 2012).

For AKL1 (Brockwell, Ampikaipakan et al. 2014) total 78 patients were selected to study the effect of AKL1, in UK at eleven sites/practices; out of these, 33 (42%) patients were enrolled in the study at the University of East Anglia site, and 32 of the 33 patients participated all four visits (one patient came only for the first three visits) (Caramori et al., 2014). The two treatment groups (AKL1 and Placebo) were similar in mean lung function, with FEV1 % ranging from 20% to 80% in the AKL1 treatment group and from 20% to 79% in the placebo group. However, it was noted that, in the AKL1 treatment group, the mean improvements in the LCQ and SGRQ (St George’s Respiratory Questionnaire scores), both absolute and relative to placebo, were greater than the MCID (minimal clinically important difference) for those measures (Willgoss & Yohannes, 2013). Moreover, the substantial improvement in the SGRQ score among AKL1-treated patients suggests there may be a beneficial effect of treatment with AKL1 (Lemmens et al., 2013).

**Leicester cough questionnaire (LCQ)**
The patient centered outcomes were determined using the Leicester Cough Questionnaire (LCQ) scores [The LCQ is a valid, repeatable 19 item self-completed quality of life measure of chronic cough which is responsive to change (Rodrigo & Neffen, 2015). It could be a useful tool in clinical trials and longitudinal studies. It can be used in clinical trials evaluating new treatments for cough and their effect on health related quality of life. In summary, the LCQ is a brief, easy to administer, and well validated chronic cough health related quality of life (HRQOL) (Birring, Prudon et al. 2003)].

**SGRQ (St. George’s respiratory questionnaire)**
SGRQ [St. George’s Respiratory Questionnaire, Disease-specific instrument designed to measure impact on overall health, daily life, and perceived well-being in patients with obstructive airways disease consisting of 50 items] (Lenkens et al., 2015). Patient-reported measures tended to be worse in the AKL1 group, with LCQ score range from 6.5 to 16.7 at baseline, compared with 10.2 to 19.8 in the placebo group. Similarly, the SGRQ, for which a higher score is worse, ranged from 36 to 86 in the AKL1 treatment group and from 20 to 73 in the placebo group.

**Roflumilast**
Phosphodiesterase 4 (PDE4) inhibitors are among the drugs that have raised hope for more effective COPD treatment. Many phase II and III randomised controlled trials (RCTs) have explored the efficacy and safety of the PDE4 inhibitors Roflumilast and Cilomilast in patients with COPD (Beauchamp et al., 2013). As a result, Roflumilast was recently approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for reducing the risk of exacerbations in patients with severe COPD and a history of exacerbations (Pinto et al., 2015).
For Roflumilast (Yu, Fain et al. 2014) patients with moderate to severe COPD with a history of exacerbations were selected, and dose of Roflumilast (1×500µg tablet per day) was approved. The outcomes, evaluated over 1 year, were moderate (a COPD event requiring outpatient treatment) or severe (a COPD event resulting in hospitalization or death) exacerbations prevented and harms. There was a probability of >50% that roflumilast presents a total advantage if the risk of severe exacerbation in a year increases 22%. Guideline developers should consider issuing different recommendations for patients at different risks for moderate and severe exacerbations.

Risk management
A benefit–harm assessment of Roflumilast following the Gail approach was conducted for decision making to use in the treatment that was developed by the National Cancer Institute. This Gail approach of assessment, analyses data on treatment effects, baseline risks and relative importance of outcomes to provide a net benefit-harm index for decision-making about a treatment or process (Singh et al., 2014). For a patient with COPD of a certain age, sex and with a certain baseline risk of exacerbations, the net benefit-harm index indicates whether Roflumilast increases or decreases the occurrence of patient centered outcomes overall (weighted by relative importance of outcomes) compared with placebo over 1 year (Montuschi et al., 2014). If there is a positive index then it indicates that roflumilast provides more benefit than harm. In sensitivity analyses, the impacts of the severity of exacerbations on the index were examined (Miravitlles et al., 2012). Details of the Gail approach are provided in the online appendix. The expected number of cases for the 11 outcomes in 10,000 men aged <65 years treated with and without roflumilast over 1 year, stratified by the patients’ baseline risk of moderate to severe exacerbations (Sin & Park, 2013). For example, in men aged <65 years with a baseline risk where 60% of patients have at least one moderate or severe exacerbation over the year, 4055 patients are expected to have at least one exacerbation in the treatment group and 4338 patients in the placebo group (accounted for mortality using Gail approach). Hence, moderate to severe exacerbations are prevented in 284 patients if 10,000 patients are treated with roflumilast (Caramori et al., 2014). However, at the same time, four cases of acute pancreatitis are expected in the treatment group while one case is expected in the placebo group. Thus, there are three excess cases of acute pancreatitis. As the patients’ baseline risk of moderate to severe exacerbations increases, more cases of exacerbation would be prevented (positive numbers) whereas the harms would remain the same (negative numbers) (Miravitlles et al., 2012).

Indacaterol
Currently available inhaled long-acting β2-agonists (LABAs), such as salmeterol and formoterol, provide bronchodilation for approximately 12 h at recommended doses and hence are administered twice daily. In chronic diseases such as COPD, compliance to treatment could be improved if the treatment regimens were simplified by reducing dosing frequency. Indacaterol is a novel, once-daily (o.d) inhaled, long-acting β2-agonist in development for chronic obstructive pulmonary disease (COPD) (Westwood et al., 2011).

For Indacaterol, significant bronchodilation was observed following administration of the first dose of indacaterol, with efficacy sustained over the full 12-week treatment period. Trough FEV1 after 12 weeks of treatment (the primary endpoint) exceeded the placebo value by more than 120mL (the pre-specified minimum clinically important difference) (Eminan et al., 2012). This value of 120mL is higher than the 100 mL described by Donohue as a difference that patients can perceive and is the midpoint of the 100-140 mL range proposed recently as a minimal clinically important difference (Struik et al., 2014). A statistically superior improvement in FEV1 for indacaterol versus placebo was also observed at all individual post-baseline time points on Day 1 and Week 12, with improvements versus placebo for FEV1 AUCs between 5 min and 1 h, 5 min and 4 h, and 1 and 4 h post-dose. These results demonstrate sustained 24-h duration of action of indacaterol on once daily dosing (Rodrigo et al., 2012). This persistence of treatment effect has also been observed in other published indacaterol studies, including a double-blind crossover study in USA patients with moderate-to-severe COPD, in which a single dose of indacaterol 150µg provided comparable 24-h trough FEV1 to twice-daily formoterol. The results of this study demonstrate that there was no loss in efficacy over the 12 weeks of treatment, with indacaterol-placebo differences maintained from Day 29 (the first trough assessment after indacaterol is known to have reached steady-state) to Week 12 in terms of trough FEV1 (Blanc, 2012).

CONCLUSION
As mentioned that COPD is a complicated disease with no specific treatment available that may eradicate the symptoms completely. 3 new treatments were researched from different articles i.e AKL1, Roflumilast and Indacaterol. But conclusions of these articles show that AKL1 needs further study with a large COPD population group for a longer period to determine its beneficial effects on severe cough in COPD patients. Similarly with Roflumilast it is concluded that use of this drug requires specific recommendation for patients at different risks for moderate and severe exacerbations. With Indacaterol, the drug showed effective bronchodilation in patients with moderate to severe COPD. It can be used as sustained release on once daily regimen as compared to other long acting bronchodilator that is given twice or thrice daily.
Thus Indacaterol may also improve the patient compliance. Indacaterol and Roflumilast have already been approved by the FDA for treatment of asthma/COPD and exacerbations. Indacaterol is available in Pakistan but Roflumilast is not readily available as yet.

REFERENCES


