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COPD Case Study

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Abstract

Chronic obstructive pulmonary disease (COPD) is a very common condition especially found among those of the older generation who have a history of smoking, a widely accepted practice where harmful effects were not known in the 1940's, 1950's, and even the early 1960's (Cummings & Proctor, 2015). The long term effects of smoking were eventually understood in the scientific community as people would present with cases of diminished lung function. The risks were published and shared with the public as the medical community better understood the phenomenon (Cummings & Proctor, 2015). After the effects of smoking on lung function became better understood, treatments were devised and experimented to help improve respiratory status. Reactive airway disease and its treatment also played a role in the development of treatment for those who had the condition labeled as chronic obstructive pulmonary disease (COPD). Some of the treatments that were developed were in the classes of medications labeled as beta 2 agonists, anticholinergics, also known as muscarinic receptor antagonists, and corticosteroids. Each agent demonstrates a specific modality to help improve air exchange in individuals whose lung function has been compromised by bronchoconstriction, the lack of functional alveoli, airway inflammation, and excessive sputum production. Here presents a case of a 78 year old female who has a history of smoking of unknown duration and presents to the family medical provider with a cough. Subsequent is a review of recently approved FDA treatment for COPD utilizing CINAHL, Pub Med, and Cochrane databases searching under the terms Breo, Trelegy, LAMA, LABA, and ICS therapy in COPD.

Background

The definition of COPD according to the American Thoracic Society (ATS) and the European Respiratory Society (ERS) is cited as a condition of limited airflow that cannot be completely reversed (Celli et al., 2014). The condition gradually progresses, being associated with chronic inflammation due to noxious gases and/or particles such as occurs with smoking, which is the most common risk factor (Celli et al., 2014). Other risk factors include public noxious gas emissions and the presence of apha1-antitrypsin deficiency (Celli et al., 2014). In COPD cholinergic mechanisms are associated with smooth muscle contraction in the form of bronchoconstriction which takes place along with the inflammatory responses in the airways. These phenomena are the primary targets of inhalation therapy that is generally recommended for patients with COPD (Buels & Fryer, 2014).

As the medical science community has become more familiar with the varying etiologic components of COPD, several things have become apparent. One component is that of alveolar surface area depletion, which involves destruction of the cells composing the alveolar epithelium. This occurs naturally during the aging process, beginning at the age of about 20 as adult lungs become fully mature and the division of cells creating the surface area of the alveoli comes to an end (Grossman & Porth, 2014). Alveolar cells then begin to go through the natural process of apoptosis without generating new cell growth, causing lung surface area to diminish as a person ages (Grossman & Porth, 2014). This process often does not result in respiratory impairment as adequate lung function is usually preserved throughout a person's life (Grossman & Porth, 2014). As the components of COPD progress, the rate of alveolar destruction is accelerated often to the point that breathing impairment occurs (Grossman & Porth, 2104).

Other etiologies that may accompany COPD are airway inflammation and sputum

production, which is the process of airway tissue swelling and exudate as inflammatory cells such as mast cells, lymphocytes, and eosinophils are manifest (Grossman & Porth, 2014). Bronchoconstriction, which is the contraction of smooth muscle encircling the airways upon stimulation from various irritants, may also be present in COPD. All of these processes disallow optimal airflow to the alveoli and obstruct gas exchange across the alveolar capillary membrane (Grossman & Porth, 2014).

The purpose for this report is to compare some of the most recent FDA approved therapies in the treatment of COPD in an attempt to provide information concerning the direction of optimal use as it pertains to the case study presented. The medications to be compared include inhaled long acting beta 2 agonists (LABAs), inhaled long acting muscarinic receptor antagonists (LAMAs), and inhaled corticosteroids (ICSs). The subsequent progress of the different classes, their improvements, and adverse effects have been briefly touched upon in this report. The medications to be compared are Trelegy Ellipta and Breo Ellipta which are long acting medications used in the treatment of COPD. Breo Ellipta was the first agent of the two to be FDA approved in 2013, and contains the combination of two active ingredients fluticasone furoate, a corticosteroid (ICS), and vilanterol, a long acting beta 2 agonist (LABA). Trelegy Ellipta, which was FDA approved in 2017, also contains fluticasone furoate and vilanterol with the additional agent of umeclidinium which is a long acting muscarinic receptor antagonist (LAMA). Both agents are designed to be effective for a period of 24 hours and are generally prescribed once a day. As COPD has different levels of severity and particular aspects, the objective is to determine the optimal regimen for the varying presentations of chronic airway obstruction.

Case Study

The patient in this case report is a 78 year old female with a smoking history of unknown duration who has a health complaint of a cough. The cough comes on unexpectedly at random times during the day and at night waking her from sleep. The cough is not productive. There has been no attempted self- treatment for her cough and nothing seems to alleviate or exacerbate the tendency to cough. The patient does not have shortness of breath while lying down at night, but occasionally has mild shortness of breath with activity that is alleviated with short periods of rest. The patient also expresses that energy levels during the day have generally been good with occasional mild episodes of fatigue. The patient occasionally has mild shortness of breath with activity that is alleviated with short periods of rest. The patient has not had any chest pain at rest or with activity. All other review of systems did not show any significant findings. The patient does not report any family medical history. Pt has a history of hypertension with no other significant medical history. Pt takes 5 mg of Lisinopril daily for hypertension. Physical exam of the patient reveals a pleasant elderly woman who appears alert, oriented, and cooperative. Skin shows no bruising or lesions. Head is normocephalic. Conjunctiva are normal. Tympanic membranes are pearly gray and clear. No inflammation of ear canal or tenderness to pinna and auricle. Septum is midline. Oropharyngeal area reveals pink mucosa with exudate. Neck is supple and non-tender with no masses or thyromegaly. Heart sounds reveal a regular rate and rhythm with no murmur, gallops, or clicks. Cap refill is < 3 seconds. No edema to extremities. Breath sounds are clear in all lung fields. Patient's gait is slightly uneven and she needs some assistance to get up to the exam table. Chest x-ray reveals clear lung fields and a heart shadow within expected limits. CBC shows values are within expected limits.

While the cough described in this case may be related to the Lisinopril that she is taking

for her hypertension, since a cough is a common side effect of angiotensin-converting enzyme (ACE) inhibitors, other possibilities may also be present such as a mild manifestation of COPD given that she has a history of smoking, is 78 years of age, and occasionally becomes short of breath with activity. While spirometry testing was not ordered for this patient at this time, future visits may warrant such testing especially if her shortness of breath increases in either the number of episodes or the duration of those episodes. The diagnosis of COPD would require an affirmation of airflow limitation or obstruction that is not completely reversible with the administration of a bronchodilator along with a history of exposure to potentially causative agents such as tobacco smoke (Celli et al., 2014).

Literature Review

The initial intention was to review Breo Ellipta and Trelegy Ellipta specifically. However, studies on these agents were not found other than initial trials that allowed FDA approval. Therefore focus was placed on the more extensive literature regarding similar classes of agents and their combinations in inhaled form, focusing on the advantages and disadvantages of the different combinations of agents.

Advantages and Disadvantages of LABA/ICS Combination

Advantages: LABA/ICS combination therapy advantages encompass the positive elements of steroid and beta 2 agonist therapy. As both long acting beta 2 agonists (LABAs) and inhaled corticosteroids (ICSs) have been used in the treatment of COPD for several years, studies have been conducted comparing LABAs alone with the use of LABA/ICS combination agents.

In Nannini, Lasserson, and Poole (2012) a Cochrane review of 14 studies examining the comparison was made involving 11,794 participants with severe COPD. COPD exacerbations

were less among participants using combination LABA/ICS therapy compared to LABA alone showing one exacerbation per year per person for those using a LABA agent and 0.76 exacerbations per year per person for those patients using a LABA/ICS combination agent (Nannini, Lasserson, & Poole, 2012). This review also showed evidence of improved quality of life as determined by utilizing the St George's Respiratory Questionnaire (SGRQ) for those who used combination LABA/ICS agents as compared to LABAs alone (Nannini, Lasserson, & Poole, 2012).

Another possible advantage of the combination LABA/ICS agent such as fluticasone furoate/vilanterol, which are two agents found in Breo Ellipta and Trelegy Ellipta, is that of a synergistic effect with both agents working together to enhance efficacy (Bateman, 2014). The mechanism involved in this is not fully understood (Bateman, 2014). LABA/ICS combination therapy also has the ICS benefit of enhancing cell surface receptor expression and hence the transcription of the beta2- adrenoceptor gene (Hidalgo, Celis, Rojas-Reyes, & Dennis, 2016). LABAs have also been shown to increase the anti-inflammatory effect of the ICS in the process of translocating glucocorticoid receptors from cell cytoplasm to the cell nucleus after corticosteroid activation (Cazzola, 2010).

While the specific LABA agent found in Trelegy and Breo, Vilaterol, has few study results as a stand-alone agent, clinical trials do reveal that with Vilaterol inhaled by itself FEV_1 results show an average increase of 82 ml after 84 days of treatment as opposed to 116 ml increase in FEV_1 when combined with the ICS Fluticasone Furoate (NIH, 2018).

Disadvantages: LABA/ICS combination inhalers have some of the disadvantages of corticosteroid use in general such as increased risk for infection. Participants using LABA/ICS combination inhalers contracted pneumonia more often compared with LABA alone in 12

studies with 11,076 people (Nannini, Lasserson, & Poole, 2012). This review showed a 4% annual risk for combination therapy and 3% risk for LABA alone (Nannini, Lasserson, & Poole, 2012). While these results show an increase in pneumonia, there was no documented significant difference in hospitalizations or mortality rates (Nannini, Lasserson, & Poole, 2012).

In the comparison of COPD patients using LABA/ICS combination vs LAMA alone studies show an increased number of deaths using the LAMA agent compared to the use of a LABA/ICS (Welsh, Cates, & Poole, 2013). All cause hospital admissions have been shown to be increased in the LABA/ICS users compared to those using the LAMA alone with no statistically significant difference in the rate of exacerbations or hospitalizations due to exacerbations (Welsh, Cates, & Poole, 2013). Antibiotic treatment, however, has been shown to be more frequent in those patients who use LABA/ICS inhalers, which correlates with a higher rate of pneumonia in LABA/ICS users compared to those who use LAMAs alone (Welsh, Cates, & Poole, 2013). In light of the above data concerning LABA/ ICS use, the approach should be to practice caution, especially in long term therapy to avoid exacerbations of pneumonia and an increased need for antibiotics.

Advantages and Disadvantages of LABA/LAMA Combination

Advantages: Karakiulakis & Roth (2012) expounded on the role of the inflammatory mediators and muscarinic receptors in COPD. These receptors mediate signaling of the natural ligand found in the cell, acetylcholine, which controls many organ physiological peripheral and central neural responses. These muscarinic receptors in the lung are present in the fibroblasts, epithelial, and smooth muscle cells affecting smooth muscle contraction, mucus secretion, and inflammation. The use of antimuscarinic agents blocks receptors inducing bronchoconstriction, which has been known for many years. Antimuscarinic activity has now been shown to be

associated with antiremodeling, anti-inflammatory, and antiproliferative effects as well, which can have profound implications for the COPD patient as remodeling of the small airways is one of the major pathologies (Karakiulakis & Roth, 2012). The American Thoracic Society points out a systematic review of seven randomized trials comparing LAMA agents with LABAs (Brotolome et al., 2014). The results of this review showed that the use of LAMA inhalers had a more enhanced result for reduced adverse effects, reduced COPD exacerbations, and reduced exacerbation-related hospitalizations. There was no difference in the results of all-cause hospitalizations, lung function, symptoms, or mortality (Bortolome et al., 2014).

Studies examining LABA/ LAMA combination and a LAMA or LABA alone show higher health-related quality of life utilizing the SGRQ in the use of LABA/LAMA agents when compared to either agent alone (Karner & Cates, 2012). Other recent studies involving periods of long duration have also shown that LABA/LAMA inhalers have shown favorable results when compared with ICS agents including improved FEV_1, decreased rate of COPD exacerbations, quality of life, and patient reported outcome in moderate to severe COPD (Tariq & Thomas, 2017).

Disadvantages: No significant disadvantages could be found in the administration of LABA/LAMA combination agents in the management of COPD patients.

LABA/LAMA/ICS Advantages and Disadvantages to be Determined

In an attempt to complete an overall review of the use of LABAs, LAMAs, and ICS therapy in combination the Cochrane Library team organized an editorial group labeled as the Cochrane Airways Group (Tan et al., 2016). Randomized controlled trials (RCTs) lasting 3 weeks or longer were to be included to compare patients with stable COPD and the effects of LABA/LAMA with ICS combination inhalers compared to LABA/LAMA alone. 586 records

were searched and duplicates were removed leaving 386 abstracts for assessment. While 6 studies were then reviewed for potential relevance, all of the 6 studies did not meet inclusion criteria for full-text assessment even after contacting authors in order to clarify the characteristics of the study. The conclusion made, therefore, was that there are no studies published as of November 2016 regarding LABA/LAMA inhalers in combination with ICS in the treatment of stable COPD and that there is a need for RCTs of strong design to assess the benefit of such (Tan et al., 2016).

The Future in Determining Individual Advantages and Disadvantages

Recent studies regarding LABA and LAMA medications have placed focus on gene expression of individuals to help predict agent response. In Kang et al. (2017) a study was completed with the endeavor to show predictions in the efficacy of LABA and LAMA agents for specific gene types. There were 3 gene expressions showing significant correlation with treatment improvement using LABA treatment and four gene expressions were found to correlate with improvement using LAMA treatment. Hizawa (2015) compared the improvement COPD exacerbations according to gene expressions in which some patients with a gene expression labeled Arg 16 had improved exacerbation outcomes with the administration of a LABA over patients with the gene expression labeled Gly 16. These studies demonstrate advantages some gene expressions may have in responding to LAMA and LABA agents.

As research continues to progress, predictability for positive response in different gene expressions to bronchodilator therapy in COPD patients may be revealed making tailored treatments more effective.

Conclusion

While more well designed studies are needed to examine ultra-long acting LAMA, LABA, and ICS agents including Breo Ellipta and Trelegy Ellipta, study results on the LABA, LAMA, and ICS agents that have been on the COPD treatment scene for longer periods of time can help to guide therapy choices in the treatment of COPD. The studies reviewed offer assistance in choosing optimal inhaled agents according to the following learning points:

- LABA, LAMA, and ICS agents have effectiveness in improving FEV_1, quality of life, and reduced exacerbations in COPD patients. (Trelegy Ellipta contains all 3 agents).
- A LABA inhaler combined with an ICS has yields an improved FEV_1 compared with the LABA alone (Breo Ellipta is composed of both agents).
- In addition to bronchodilation LAMA inhalers reduce the effects of airway remodeling which can be a significant factor in COPD.
- ICS agents should be administered with caution considering susceptibility to pneumonia and other unwanted side effects such as weight gain and osteoporosis.
- LAMA/LABA agents may be as or more effective as ICS combination agents in increasing FEV_1, improving quality of life, and reducing COPD exacerbations
- In the future determining gene expression may be helpful in predicting the efficacy of certain inhaled agents in the treatment of COPD as evidenced in studies of LAMA and LABA agents.

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