Role of Tiotropium as Step Up Therapy for Asthma

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Abstract

Background: To determine the role of Tiotropium as step up therapy for patients with uncontrolled asthma.

Methods: In this case control study 130 patients, with diagnosis of bronchial asthma for at least 01 year and presently on step 4 treatment and still symptomatic, were included. Sixty five patients were randomly assigned to receive Tiotropium bromide dried inhaler added to their conventional step 4 treatment, whereas 65 patients were given placebo. Patients were asked about symptomatic improvement, using mini AQLQ. Peak Expiratory Flow Rate (PEFR) was checked eight weeks after wards to document response to therapy.

Results: Mean age and duration of diagnosis of asthma was 38 years and 5.1 years, respectively in cases. Mean PEFR at admission among cases was 210 l/min (± 58.35) while it was 203 l/min (± 57.32) among controls. Frequency of nocturnal awakening were 2.98 days/ week among cases and 2.88 days/ week among controls. At week 8, frequency of nocturnal symptoms was found to be 1.6 days/week among patients on Tiotropium while it was 2.13 days/week among controls. Mean PEF was 387 l/min among Tiotropium group as compared to 305 l/min. There was statistically significant improvement in symptoms and PEFR of patients on Tiotropium as compared to controls. (p value 0.004). The differences remained statistically significant after adjusting for age and gender.

Conclusion: Tiotropium daily as maintenance treatment through dried inhaler in addition to at least high-dose inhaled corticosteroids combined with long acting B2 agonists offers significant potential to improve airway patency in patients with severe persistent asthma who are still symptomatic and obstructed on maximal therapy.

Key Words: Asthma, Tiotropium, anticholinergic.

Introduction

Asthma is an inflammatory disorder of the airways characterized by variable airflow obstruction and airway hyper responsiveness to a variety of stimuli. The goal of asthma management is control of its symptoms but it is a well documented fact that many patients do not achieve this target even after maximum doses of inhaled corticosteroids (ICS) and long acting B2 agonists (LABA).1,2 If still patients remain symptomatic then a second bronchodilator with different mechanism of action can be tried like Tiotropium bromide which is widely used for treatment of COPD.3,4 Tiotropium slowly dissociates from muscarinic receptors and hence has got long duration of action. By virtue of slow dissociation from receptors it has also got slower as well as smaller action as compared to short acting bronchodilators (SABA) and usually not used in acute Asthma.5,6 In contrast although ipratropium is not usually employed as a first-line bronchodilator to treat chronic asthma, it has been used extensively in emergency departments as adjunctive therapy with beta agonists for the emergency treatment of acute asthma exacerbations and it results in modest improvement in morning peak expiratory flow (PEF)7. Whereas Tiotropium is a newer long-acting anti cholinergic medication and a few clinical trials have been performed to study the use of Tiotropium for management of uncontrolled asthma. Preliminary evidence suggests that adding Tiotropium to medium dose inhaled glucocorticoid may be effective treatment in improving uncontrolled asthma. Although long term use of anti cholinergic drugs for Asthma is not commented in Global initiative for Asthma (GINA) guidelines but many studies showed beneficial role of Tiotropium when used as maintenance long term therapy.2,8,9,10,11 Recently in Peter et al study it has been proven that in mild to moderate asthma uncontrolled with only low dose ICS the addition of Tiotropium to ICS yielded much superior improvement in morning PEF as well as symptoms and asthma control days as compared to doubling the dose of ICS beclomethasone.12 It is also noted that Tiotropium was not found inferior to Salmeterol. However role of Tiotropium in severe uncontrolled asthma is still unexplored extensively.13 The present study can be taken as one of the pioneer work on this topic.
Patients and Methods

This case control study was carried out in department of Pulmonology, Military Hospital Rawalpindi, from August 2011 to December 2012. A total of 130 patients of uncontrolled bronchial asthma on step 4 treatment by consecutive sampling, admitted to medical wards with worsening of their symptoms, were enrolled. Diagnosis of asthma was based on compatible history and physical examination supported by spirometry demonstrating airflow obstruction with significant reversibility (documenting more than 12% change in FVC and 200 ml in FEV1 post bronchodilator) and there is no alternative explanation for the symptoms and airflow obstruction (eg, smoking, bronchiectasis). Inclusion criteria included age 40-75 years of age, atleast 01 year history of asthma, both male and female gender, non-smokers, no antibiotic treatment in past 02 weeks. Patients with COPD, previous history of tuberculosis, resting heart rate more than 100 beats per minute, glaucoma, prostatic enlargement, hypersensitivity to anti cholinergic, and those with underlying malignancy were excluded from study. Prior to enrollment, each patients detailed history, clinical examination, pulse oximetry, lung function tests were reviewed. All the participants were given step 4 conventional treatment with ICS, LABA, methylxanthines and leukotrienes receptor antagonist. Out of 130 patients, 65 patients were randomly selected to be given Tiotropium 18 ug daily, while 65 patients were given placebo. The primary outcome was improvement in symptoms as document by mini AQLQ (asthma quality of life questionnaire). Secondary outcomes were improvement in PEF recording. Frequency of nocturnal symptoms was found to be 1.6 days/week (± 1.13) among patients on Tiotropium while it was 2.13 days /week (± 1.8) among controls. Mean PEF was 387 l/min (± 65) among Tiotropium group as compared to 305 l/min (± 54) (Table 2). There was statistically significant improvement in symptoms and PEF recording. Frequency of nocturnal symptoms was 2.98 days/week (± 1.78) among cases and 2.88 days/ week (± 1.82) among controls. At week 8, the study participants were reassessed for symptoms improvement and PEF recording. Frequency of nocturnal symptoms was found to be 1.6 days/week (± 1.13) among patients on Tiotropium while it was 2.13 days /week (± 1.8) among controls. Mean PEF was 387 l/min (± 65) among Tiotropium group as compared to 305 l/min (± 54) (Table 2). There was statistically significant improvement in symptoms and PEF of patients on Tiotropium as compared to controls. (p value 0.004). The differences remained statistically significant after adjusting for age and gender.

Discussion

Although most patients of asthma are usually controlled with step 4 and 5 treatments but some still remain uncontrolled. These patients develop frequent exacerbations, drain health resources with progressive
decline in patient’s health. This study was designed to address this subset of patients and demonstrated significant improvement in both symptoms as well as pulmonary function in patients treated with Tiotropium. Both dried and mist inhalers of Tiotropium are used for chronic obstructive airway disease but now it has been shown that mist inhaler increases cardiovascular mortality in patients of COPD. This study documents a clear superiority of Tiotropium compared with controls in asthmatic patients whose symptoms are not controlled with at least ICS plus LABA treatment in terms of primary and secondary spirometry end points and symptomatology. Our results are comparable with Peter et al study in which milder asthma subjects on low dose ICS were selected and here addition of Tiotropium produced the similar results. It also support the results of Michael G et al study however in this study selected patients were between 18 to 75 years of age and all patients were using high-dose ICS >800 mg of budesonide or equivalent and a LABA and then they were given Tiotropium for eight weeks as compared to our study where we only administered Tiotropium for two weeks. Similarly effect of Tiotropium was comparable with that of COPD patients who were given this without LABA in Casaburi R et al as well as Tashkin DP et al studies. In animal models of allergic asthma it has been shown that Tiotropium also has got anti inflammatory effects but in our study we only focused towards spirometry and symptomatic outcomes and eosinophilia as well as other markers of inflammation were not evaluated. Role of Tiotropium in combination with ICS and LABA as triple therapy is yet to be established for efficiency and safety. Only one of such study is available thus we also suggest that this triple regimen in treatment of uncontrolled asthma should also be studied in future with larger population size.

References