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Does Short Term Atorvastatin Treatment Improve Symptomatic Control in Patients with Mild to Moderate & Uncontrolled Asthma?

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ABSTRACT

Introduction: Asthma is a chronic disease characterized by recurrent episodes of breathlessness and wheezing. Keeping in view the problems in asthma control and side effects of available medication, there is a need for alternative treatments with better efficacies and fewer side effects. Atorvastatin is a statin that blocks HMG CoA reductase enzyme found in the liver, inhibiting the synthesis of cholesterol. Blockade of this pathway also inhibits production of GTPases which are involved in airway inflammation, airway remodeling and contraction of smooth muscles of the bronchi.
Aims & Objectives: To evaluate the symptomatic control in mild to moderate and uncontrolled asthma patients using standard treatment versus its combination with atorvastatin.
Place and duration of study: This study was conducted in Pulmonology Department of Lahore General Hospital; Lahore over a 4-week duration from October 2018 till February 2019.
Material & Methods: Patients of mild to moderate and uncontrolled asthma were enrolled in this study based on inclusion and exclusion criteria. Patients were divided into two groups by lottery method, Group 1 and Group 2, with 34 patients in each group. Group 1 was continued with standard therapy of asthma and the Group 2 was administered atorvastatin 40 mg, once daily in addition to standard therapy for 4 weeks. The control of asthma before and after treatment was assessed based on Global Initiative for asthma (GINA) guideline questionnaire score. SPSS (Statistical Package for Social Sciences) version 22 was used for analysis of data. P-Value < 0.05 was taken as significant.
Results: Nonsignificant results were obtained when comparison between the groups was made based on GINA guidelines questionnaire score by Mann Whitney Utest
Conclusion: It was concluded that atorvastatin has no role in symptomatic control in patients of mild to moderate and uncontrolled asthma.

Keywords: Asthma, atorvastatin, GINA guidelines questionnaire score

INTRODUCTION

Asthma is a syndrome characterized by airflow obstruction and a special type of airway inflammation resulting in excessive narrowing followed by reduced airflow leading to symptoms of wheeze. Airway narrowing is mostly reversible but, in some patients, there may be an element of irreversible airflow obstruction[1].

The key features of asthma include pulmonary inflammation and airway hyper responsiveness (AHR)2. The inflammatory process is largely restricted to the conducting airways but as the disease becomes more severe and chronic, the inflammatory infiltrate spreads both proximally and distally to include the small airways and in some cases adjacent alveoli[3].

Asthma control and severity of disease can be measured both subjectively and objectively. Traditionally asthma treatments have been categorized according to symptoms and spirometry/peak flow measurements.[4]The management of asthma depends on two specific factors, first is to reduce possible triggering factor and secondly use of proper medication[5]. According to treatment guidelines, inhaled corticosteroids are being considered as first-line therapy for persistent asthma of all severities. Once the asthma control is achieved, the guidelines further recommend the "stepping down" of therapy to minimize the adverse effects of medication[6]. The important long term control asthma medications include anti-inflammatory agents, long-acting bronchodilators, and leukotriene modifiers. The important quick relief

medications are short acting bronchodilators and systemic corticosteroids[7]. Newer treatment strategies involve Rho Kinase inhibitors which cause relaxation of airway smooth muscle and bronchodilation by blocking small GTPases like Rho Kinase which partake in broncho-constriction, airway inflammation, airway fibrosis, airway remodeling and neuromodulation[8].

One of the most prescribed drugs worldwide, statins, are cholesterol-lowering agents used to manage and prevent cardiovascular and coronary heart diseases. Many versatile actions of statins have come to know including their immune-modulatory and anti-inflammatory properties[9].

Statins, inhibitor of hydroxyl-methylglutaryl coenzyme A (HMG-A) reductase, inhibit the mevalonate pathway and the synthesis of downstream intermediates including farnesyl pyrophosphate (FPP) and geranyl geranyl pyrophosphate (GGPP), which post-translationally modify small guanosine tri-phosphatases (GTPases). GTPases may play a role in the patho-physiology of asthma because they could augment airway smooth muscle contraction and proliferation and increase airway hyperresponsiveness[10].

Several studies have been done to see the effect of statins in asthma which have demonstrated controversial results[11]. This study is not yet done in our Pakistani population despite a sizable number of asthma patients. So, there is a need for a local study to establish role of statins in control of asthma symptoms.

MATERIAL AND METHODS

This project was approved by Ethical Committee of Post Graduate Medical Institute, Lahore vide letter number 938/EC/PGMI/2018. Trial was registered with research registry online (Research registry unique international number-3788, Registration date- March 07, 2018). Study was done in the Department of Pulmonology and Sleep Medicine, Lahore General Hospital, Lahore from October 2018 till February, 2019. More than 68 clinically diagnosed nonsmoker asthmatic patients between 18 to 60 years of age with no history of lower respiratory tract infection in past six weeks were enrolled[12].Patients already taking statins, having liver disease, musculoskeletal problems, history of drug reactions or pregnancy were excluded.

68 patients who fulfilled the criteria were randomized by third person into two groups. One control group and the other one case group with 34 patients in each group. There was concealment of allocation. Prescribing doctor knew allocation at the time of prescribing medication. The symptomatic control of asthma was assessed at the start and end of the study based on questionnaire of Global initiative for asthma (GINA) Guideline. Patients were categorized as well controlled, partially controlled and uncontrolled on the basis of guidelines questionnaire score as given in (Table-1)[13].

Data was entered in questionnaire after informed written consent. A 4-week treatment plan was instituted to patients according to their stage of asthma. In Group 1 well controlled asthma patients received regular treatment of (low dose inhaled corticosteroids, plus short acting beta 2 agonist purchased from (Highnoon Laboratories) & (Getz Pharma) respectively. While partially controlled patients received inhaled corticosteroids plus long-acting beta 2 agonist. Uncontrolled patients received both oral and inhaled corticosteroids plus long-acting beta 2 agonists and leukotriene receptor blockers which were purchased from (Hilton Pharma)

Whereas in Group 2, 40 mg /day Atorvastatin (Highnoon Laboratories) was added as a single dose by oral route for the same time period of 4 weeks in addition to regular treatment of asthma stated above. Normal levels of liver function tests were ensured in every patient of case Group 2 before prescribing Atorvastatin. All the medicines were provided to the patients throughout the study. They were counseled regarding any possible side effects of the therapy and when to contact the department in case of any side effect. Daily telephonic reminder was given to ensure good compliance. Patients were advised to visit after two weeks of treatment for follow up of adverse effects and assurance of compliance of patients.

SYMPTOM CONTROL	**LEVEL OF ASTHMA SYMPTOM CONTROL**
In the last 4 weeks, has the patient had:	**Well Controlled** (None of these) **Partially Controlled** (1-2 of these) **Uncontrolled** (3-4 of these)
Day time asthma symptoms more than twice a week **Yes/ No**	
Any night waking due to asthma **Yes/ No**	
Reliever needed for symptoms more than twice a week **Yes/No**	
Any activity limitation due to asthma **Yes/No**	

Table-1: GINA Assessment of Asthma Control

Statistical Analysis:

Data was analyzed by SPSS (Statistical Package for Social Sciences) version 22. Normality of data was confirmed by Shapiro Wilk test. Qualitative variables were presented in percentages, frequencies and graphs. Comparison among groups for qualitative variables was done with Mann Whitney U test. Comparison within a group over time for qualitative variables was done with Wilcoxin signed rank test. P-value <0.05 was considered statistically significant and P-value <0.001 was considered as highly significant.

RESULTS

Based on GINA guidelines questionnaire, data was collected at the start and end of study (4 weeks). According to these guidelines disease status of the patients was labeled as well controlled, partially controlled, and uncontrolled. Frequency of patients with well controlled, partially controlled and uncontrolled disease status before and after the treatment is given in Fig-1.

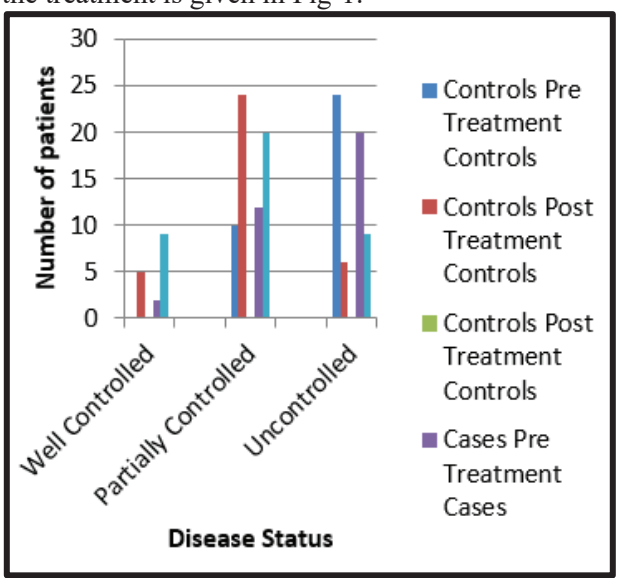

Fig-1: Graphical presentation of frequency of patients with disease status according to GINA guideline assessment in controls (group 1) and cases (group 2).

DISCUSSION

According to the GINA guidelines, disease status of well controlled, partially controlled, and un-controlled patients of asthma was evaluated based on diurnal variation, nocturnal variation, activity limitation and exacerbation of disease[14]. Disease status of patients in both the groups was further assessed before and after the administration of treatment along with any improvement in the quality of life of patients based on symptom control.

Results of GINA guidelines score were presented as frequency and percentages of patients in each category (well controlled, partially controlled and uncontrolled) before and after the treatment. Improvement in asthma status was observed in both the groups after use of drugs which was evident by a significant increase (P-value < 0.05) in the frequency and percentage of patients in partially controlled and well controlled category compared to same frequencies and percentages in pretreated patients and a significant decrease (P-value < 0.05) in uncontrolled category. In case of comparison between the groups regarding improvement in quality of life, no significant difference (P-value > 0.05) was observed showing no potentiating effect of addition of Atorvastatin to standard therapy in the improvement of asthma status of patients.

Findings of our study have some concurrence to a study done in Glasgow, UK[15] where asthma control questionnaire (ACQ) score was used as a tool for assessing the therapeutic role of atorvastatin in the control of atopic asthma but no significant improvement was observed in the symptom control even after a treatment of 8 weeks. Contrary to our study findings statistically significant improvement in asthma control with Atorvastatin use was observed in Indian population according to asthma control questionnaire score (ACQ) result[16]. In a Turkish study, no significant role of Rosuvastatin in the improvement of quality of life of patients was observed based on asthma control test (ACT) and asthma quality of life (QoL) test results[17]. Steroid sparing role of Simvastatin in asthma treatment was studied in a placebo controlled cross over trial in New Zealand. Although no steroid sparing role was established in this trial but different to our study results slight improvement in asthma symptoms assessed by asthma control questionnaire (ACQ) score was observed in simvastatin treated group compared to placebo control group[18].

These controversial results in the present study are, may be because of small sample size and short study duration or may be due to poor compliance by the patients. There is a need for more studies to be carried out on large scale with increased number of patients and prolong duration of treatment as the immunomodulatory and anti-inflammatory properties of statins cannot be denied based on literature available. It is suggested

that further clinical work should be done on large scale and with increased number of patients.

CONCLUSION

In the light of results in the present study, it is concluded that atorvastatin has no effective role in improving the symptomatic control of mild to moderate and uncontrolled asthma when used on short term basis e.g., for 4-weeks.

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