e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2022; 14(12); 1075-1081

Original Research Article

# A Study of Efficacy and Safety of Atorvastatin as Add on Therapy in the Treatment of Moderately Severe Asthma

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**Received: 03-10-2022 / Revised: 25-10-2022 / Accepted: 21-11-2022**
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**Conflict of interest: Nil**

**Abstract**

**Background:** Airway wall inflammation and asthma are very closely related. Statins appear to inhibit signaling molecules, which causes a reduction in gene expression and reduces the stability of lipid raft formation, which has effects on the activation and control of the immune system. By lowering cytokine, chemokine, and adhesion molecule production, both these effects affect cell death or proliferation.

**Methods:** A total of n=60 cases were included in the study based on the inclusion and exclusion criteria they were randomly allotted equally (n=20) to one of the three groups. Detailed medical history and demographic details were obtained from all patients who gave informed consent for the study. The investigations included complete blood picture, ESR, Hb, Absolute eosinophil counts, RBS, Renal function tests, Liver function tests, lipid profile, ECG, Chest X-ray, Spirometry, and Asthma control score (ACS).

**Results:** the asthma control scores were compared in the three different groups of the cases at different intervals at the baseline there was no statistically significant difference between the groups. The ACS subjective score is significant after 4 and 8 weeks of study for groups II and III. In between groups, there was statistical significance between standard group I with groups II and III. Also, there was a statistical difference between groups II and III suggesting that an increase in atorvastatin dose from 10 to 20 mg is beneficial in chronic asthmatics.

**Conclusion:** we conclude that atorvastatin is effective as an adjuvant in the management of chronic stable asthma (moderate-severe). As an adjunct medication, atorvastatin 20 mg is more effective in treating asthma than atorvastatin 10 mg once a day. The dosages of 10 mg and 20 mg of atorvastatin were proven to be safe for chronic stable asthmatics.

**Keywords:** Asthma, Statins, Asthma control score, $FEV_1$, PFR



## Introduction

An estimated 300 million people globally suffer from asthma, making it a serious issue. In many nations, 1% to 18% of the population suffers from asthma. According to the World Health Organization, asthma costs the world 15 million disability-adjusted life years (DALYs) per year or 1% of all diseases. An estimated 250,000 people die from asthma-related causes each year throughout the world. [1] Airway wall inflammation and asthma are related. In bronchoalveolar lavage fluid and airway

wall biopsies from asthmatic patients, have an increased number of several types of inflammatory cells, most notably eosinophils but also basophils, mast cells, macrophages, and some types of lymphocytes. It is yet unclear how bronchial inflammation affects asthmatic symptoms. Although there are many forms of asthma (allergic versus non-allergic), all asthmatic airways have some characteristics of airway inflammation. The production of interleukin 4 (IL-4), IL-5, and IL-13 are increased as a result of the T-helper type 2 (Th2) phenotypic bias of the lymphocytes involved in asthma pathogenesis. IgE production in B cells is aided by the IL-4 produced by Th 2 cells and basophils. Support for eosinophil survival is provided by IL5. Chronic inflammation over time results in mucous membrane loss and rearrangement, epithelial shedding, and Subepithelial fibrosis and smooth muscle hyperplasia are two common examples of subepithelial fibrosis, hypersecretion, and airway wall remodeling. [2] By blocking β-Hydroxy β-methylglutaryl-CoA (HMGCoA) reductase, statins lower cholesterol levels and are a well-established component of the management of the atherosclerotic disease. Statins have been found to have anti-inflammatory effects. Statins appear to block signaling molecules, which results in a downregulation of gene expression, and to decrease the stability of lipid raft formation, which has implications for immunological activation and regulation. Both of these actions have an impact on cell death or proliferation by reducing the production of cytokines, chemokines, and adhesion molecules. [3] Simvastatin decreased the amount of total inflammatory cells, including macrophages, neutrophils, and eosinophils in the fluid from bronchoalveolar lavage in allergic asthmatic mouse models. In clinical investigations, patients who received statin medication after lung transplantation fared better than those who did not. The fact that statin use decreased myofibroblast function most likely reflected this outcome. 3 Ras, a tiny guanosine triphosphate (GTP)-binding protein and a crucial signaling molecule operating downstream of growth hormones, appears to be the major cell signaling molecule impacted by statins. Through an alteration of Ras localization to the inner plasma membrane of fibroblasts, lovastatin can suppress the activation of Ras. 3 Furthermore, so-called "bench" studies from recent fundamental research have shown that statins have a strong immunomodulatory effect on the control of T1/T2 polarisation in animals or in vitro models. [4] This study was undertaken to assess the efficacy and safety of Atorvastatin in different doses (10mg, 20mg), along with the conventional regimen, in chronic stable asthma (mild, moderate) in our community, keeping in mind the aforementioned evidence on the anti-inflammatory and immunomodulatory effects of statins. This study was conducted on chronic asthmatic patients visiting the Department of pulmonology of our institute to evaluate the efficacy of Atorvastatin as an adjuvant in the treatment of chronic moderate-severe, stable asthma.

## Material and Methods

This cross-sectional study was conducted in the Department of Pulmonology, Prathima Institute of Medical Sciences, Naganoor, Karimnagar. Institutional Ethical approval was obtained for the study. In local vernacular, the study's goal, methodology, and potential adverse effects were described. Those who were willing to participate in the study voluntarily were provided their written informed permission in the required format and the local language. Illiterate patients provided a left thumb imprint. This was carried out in front of a witness who was not biased.

## Inclusion criteria

1. Aged above 18 – 50 years
2. Males and females
3. Diagnosed with chronic moderate-severe asthma

4. With symptoms of asthma for more than one year
5. Using bronchodilators daily and steroids with night or early morning symptoms
6. Willing to participate in the study voluntarily

**Exclusion criteria**

1. Acute Asthma
2. Other respiratory infections, inflammatory diseases,
3. autoimmune diseases.
4. Abnormal CPK, liver transaminases, and renal diseases.
5. Already on statin therapy.
6. Unstable asthma
7. Previous statin sensitivity, myopathy, or myositis
8. Diabetes mellitus
9. H/o chronic systemic illness
10. Pregnant and lactating females

A total of n=60 cases were included in the study based on the inclusion and exclusion criteria they were randomly allotted equally (n=20) to one of the three groups

Group I: Standard therapy (Salbutamol 4 mg BD+Deriphylline 100mg TID)

Group II: Standard therapy + Atorvastatin 10 mg

Group III: Standard therapy + Atorvastatin 20 mg

Detailed medical history and demographic details were obtained from all patients who gave informed consent for the study. The investigations included complete blood picture, ESR, Hb, Absolute eosinophil counts, RBS, Renal function tests, Liver function tests, lipid profile, ECG, Chest X-ray, Spirometry, and Asthma control score (ACS).

Drugs were given for two weeks. They were requested to return the empty packs after the first two weeks to assess their compliance before being given the medication for the next two weeks. For 8 weeks, the same approach was used. Any adverse effects that patients reported, or doctors saw during the trial were noted. The patient was instructed to notify the investigator right away if any negative effects occurred.

*Follow-up*: the first follow-up was at the end of 4 weeks and the second follow up at the end of 8 weeks. During the follow-up, efficacy was assessed by estimation of FEV1, and PEFR, from baseline measurements, lab parameters AEC and ESR, and asthma control scores which are based on

- Work limitation due to asthma during the past 4 weeks
- Shortness of breath during the past 4 weeks
- Night or early morning symptoms during the past 4 weeks
- Rescue medication needed during the past 4 weeks
- Self-rating of asthma during the past 4 weeks

*Statistical Analysis:* Data collection and analysis were carried out using an MS Excel spreadsheet and SPSS version 22. (Chicago, IL, USA). While qualitative factors were expressed in proportions and percentages, quantitative data were expressed using means and standard deviations. To determine the difference between the proportions, ANOVA was performed.

**Results**

In the study, the group I (n=20) cases were having a mean age of 39.65 ± 6.65 years. In the group II (n=20) case the mean age was 38.05 ± 5.52 years and in group III (n=20) the mean age was 37.50 ± 4.66 years. The groups were homogeneous based on the mean age distribution and the p-values were not significant.

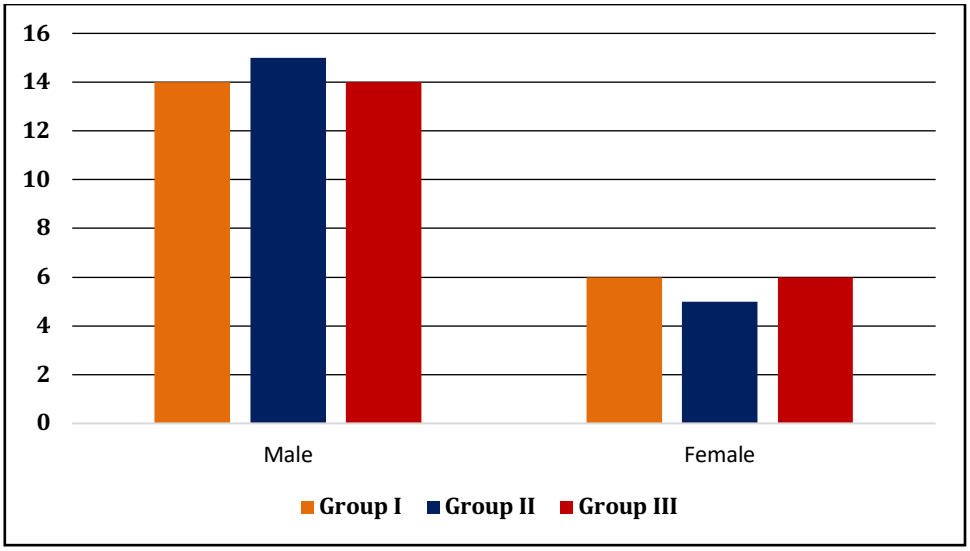


**Figure 1: Distribution of cases based on sex in different groups of the study**

A total of n=43(71.67%) were males and n=17(28.33%) were females. The distribution of males and females has been depicted in figure 1. In group I out of n=20 cases n=14(70%) cases were males and n=6(30%) cases were females' similar distribution was also present in group III. In group II out of n=20 cases, n=15(75%) cases were males and n=15(25%) cases were females. There was no statistically significant difference among groups in sex distribution. Based on the duration of the illness the mean duration of illness in group I was 4.66 ± 1.0 years group II was 5.5 ± 1.5 years and group III was 4.22 ± 1.2 years.

**Table 1: Comparison of Asthma control scores in the three groups at different intervals**

| | Baseline score | After 4 weeks | After 8 weeks | P values |
|---|---|---|---|---|
| Group I | 18.24 ± 1.1 | 18.81 ± 0.55 | 19.01 ± 0.55 | 0.125 |
| Group II | 17.52 ± 0.89 | 18.92 ± 0.61 | 21.92 ± 0.67 | 0.045 * |
| Group III | 18.77 ± 9.21 | 19.89 ±0.43 | 22.37 ± 0.51 | 0.001* |

In table 1 the asthma control scores were compared in the three different groups of the cases at different intervals at the baseline there was no statistically significant difference between the groups. The ACS subjective score is significant after 4 and 8 weeks of study for groups II and III. In between groups, there was statistical significance between standard group I with groups II and III. Also, there was a statistical difference between groups II and III suggesting that an increase in atorvastatin dose from 10 to 20 mg is beneficial in chronic asthmatics.

**Table 2: Comparison of $FEV_1$ (L)in the three groups at different intervals**

| $FEV_1$ (L) | Baseline score | After 4 weeks | After 8 weeks | P values |
|---|---|---|---|---|
| Group I | 1.95 ± 0.55 | 1.99 ± 0.64 | 1.95 ± 0.36 | 0.432 |
| Group II | 1.68 ± 0.64 | 2.01 ± 0.35 | 2.16 ± 0.41 | 0.171 * |
| Group III | 1.88 ± 0.48 | 2.27 ± 0.41 | 2.55 ± 0.57 | 0.001* |

* Significant

Table 2 shows that FEV1 at 8 weeks is statistically significant for the group (i.e., with a higher dose of atorvastatin). There is a statistical significance between groups I and III which again shows that a higher dose of atorvastatin is beneficial for asthmatics.

**Table 3: Comparison of PEF (L/min) in the three groups at different intervals**

| PEF(L) | Baseline score | After 4 weeks | After 8 weeks | P values |
|---|---|---|---|---|
| Group I | 348.99 ± 61.22 | 425.66 ± 47.30 | 422.35 ± 37.95 | 0.351 |
| Group II | 395.64 ± 59.61 | 438.19 ± 39.73 | 439.55 ± 38.01 | 0.145 |
| Group III | 386.71 ± 53.22 | 421.36 ± 35.66 | 440.37 ± 36.63 | 0.05 |

* Significant

Peak Expiratory Flow (PEF) at baseline is not significant in all the groups as given in table 3. PEF at 2 months is statistically significant in group III (i.e., with a higher dose of atorvastatin) There is a statistical significance between groups I and III which shows that a higher dose of atorvastatin is beneficial for asthmatics.

**Table 4: Comparison of Absolute Eosinophil Counts in ($mm^3$) in the three groups at different intervals**

| AEC /$mm^3$ | Baseline score | After 4 weeks | After 8 weeks | P values |
|---|---|---|---|---|
| Group I | 460.25 ± 50.27 | 440.83 ± 47.80 | 419.67 ± 38.84 | 0.122 |
| Group II | 511.36 ± 53.94 | 451.27 ± 45.55 | 401.26 ± 40.02 | 0.020* |
| Group III | 541.19 ± 49.92 | 420.15 ± 41.71 | 399.97 ± 65.35 | 0.004* |

* Significant

Table 4 shows the absolute eosinophil counts of the three groups at different intervals. A critical analysis of table 4 shows the values of AEC in group I did not significantly improve at 8 weeks. However, the values were significantly improved in group II as well as group III. Table 5 depicts the adverse events reported in the different cases during the duration of the study. It was observed that the distribution of adverse events was equal in all three groups. Most of the reported adverse events were mild and did not require any modification of dosage used by the patients in the study.

**Table 5: Depiction of Adverse events reported in the different groups**

| | Group I | Group II | Group III |
|---|---|---|---|
| Myalgia | 0 | 1 | 0 |
| Nausea | 1 | 1 | 1 |
| Dyspepsia | 1 | 0 | 1 |
| Others | 0 | 1 | 1 |

## Discussion

Chronic inflammatory lung illness known as asthma is characterized by recurrent airway blockage and hyperresponsive bronchial tissue. [5] Studies that employed autopsy specimens to examine the macroscopic, morphologic and histologic alterations inside the big asthmatic airways supported the idea that inflammation is a significant contributor to asthmatic pathology more than 100 years ago. [6] It is now well acknowledged that the distal lung [7, 8] and the lung parenchyma are also sites of recruitment of inflammatory cells in asthmatics, particularly eosinophils and T lymphocytes. [9] T Helper-2 cytokines, chemokines, and pro-inflammatory mediators, such as cyclooxygenase metabolites, are prevalent in this remote location. [10] Any alterations that arise in the distal lung and parenchyma of asthma patients are likely to have a significant impact on the pathophysiology and management of this condition. Recent research demonstrated the critical role of the monomeric GTP-binding protein RhoA in the contraction of bronchial smooth muscle (BSM). For the therapy of asthmatic

airway hyperresponsiveness, RhoA and its downstream have been suggested as novel targets. By reducing geranylgeranyl pyrophosphate levels, statins are known to prevent RhoA from functioning. [11]

A retrospective cohort design comprising 854 consecutive patients (mean age 70.8 years, 51.5% female) with a diagnosis of COPD exacerbation was included in the research after discharge from a Norwegian teaching hospital. Median follow-up lasted 1.9 years. After a COPD exacerbation, statin therapy was linked to increased survival. [12] The present study on chronic stable asthmatics receiving normal treatment considers the pleiotropic effects of statins mentioned in the aforementioned studies. All patients had spirometry performed at 0, 4, and 8 weeks. In our investigation, individuals receiving 20 mg of atorvastatin had statistically significant differences in their results (Group III). At 8 weeks, group III cases had FEV1 levels dramatically increased. In comparison to group I, which experienced a slight increase at 4 weeks from baseline and no significant increase at 8 weeks from baseline, group III's FEV1 improvement was 39.36 ml at 4 weeks from baseline and 68.50 ml at 8 weeks from baseline. The PEF value increased similarly in group III at the end of 8 weeks as compared to the group I cases (p=0.05). The other atorvastatin trials likewise showed an improvement in lung function. [13] The absolute eosinophil count which is a marker of inflammation in chronic asthma has declined in group II and Group III cases at the end of 8 weeks when compared to the similar cases of group I given in table 4. The asthma control score was applied to the subjective evaluation in this study. In comparison to group II and III patients receiving conventional medication alone (group I), there was an increase in score, which may indicate an improvement in asthma symptoms. The frequency of COPD exacerbations and intubations in patients on statin treatment was examined in research at Regional Medical Center in the United States. [14] the average number of exacerbations among COPD patients not taking statins was 1.59 per patient per year compared to 0.41 among patients taking statins (odds ratio 13.83, 95% confidence 4.564 to 24.01; p=0.001). [14] While in our study, the measurements of the asthma symptom score showed a significant statistical difference in groups II and C (P=0.001) at 4 and 8 weeks. We concluded that atorvastatin, at increasing dosages, can treat persistent asthma by reducing symptoms as well as lung function. Throughout the research period, no severe adverse events were reported. Myalgia, nausea, and dyspepsia, which are minor side effects that are self-limiting and do not require drug withdrawal or additional medication to treat them, were similarly distributed throughout the research groups. Thus, our study investigated the safety of atorvastatin at increasing doses of 10 mg and 20 mg in chronic stable asthma.

## Conclusion

From this study, we conclude that atorvastatin is effective as an adjuvant in the management of chronic stable asthma (moderate-severe). As an adjunct medication, atorvastatin 20 mg is more effective in treating asthma than atorvastatin 10 mg once a day. The dosages of 10 mg and 20 mg of atorvastatin were proven to be safe for chronic stable asthmatics.

## References

1. Masoli M, Fabian D, Holt S, Beasley R. The global burden of asthma: executive summary of the GINA Dissemination Committee report. Allergy 2004; 59(5): 469-78.
2. Bradley J. Undem. Goodman and Gilman's The Pharmacological basis of therapeutics. Chapter 27. Pharmacotherapy of asthma, 11th edition. McGraw-Hill 2005; 717.
3. Takizawa H. Novel strategies for the treatment of asthma. Recent Pat

Inflamm Allergy Drug Discov. 2007 Feb;1(1):13-9.
4. Barnes PJ. Asthma. In: Jameson J, Fauci AS, Kasper DL, Hauser SL, Longo DL, Loscalzo J. eds.Harrison's Principles of Internal Medicine, 20e. McGraw Hill; 2018. p. 1508-1515.
5. Dunnil MS. The pathology of asthma, with special reference to changes in the bronchial mucosa. J ClinPathol 1960; 13:27-33.
6. Curschmann H. Ueber bronchiolitis exsudative und ihr Verhaltnisszum asthma nervosum. Dtsch Arch Klin Med 1882; 32:1-34 [in German].
7. Hamid Q, Song Y, Kotsimbos TC, Minshall E, Bai TR, Hegele RG, Hogg JC. Inflammation of small airways in asthma. J Allergy ClinImmunol. 1997 Jul;100(1):44-51.
8. Minshall EM, Hogg JC, Hamid QA. Cytokine mRNA expression in asthma is not restricted to the large airways. J Allergy Clin Immunol. 1998 Mar; 101(3):386-90.
9. Kraft M, Djukanovic R, Wilson S, Holgate ST, Martin RJ. Alveolar tissue inflammation in asthma. Am J RespirCrit Care Med. 1996 Nov; 154(5):1505-10.
10. Schulman ES, Adkinson NF Jr, Newball HH. Cyclooxygenase metabolites in human lung anaphylaxis: airway vs. parenchyma. J Appl Physiol Respir Environ Exerc Physiol. 1982 Sep; 53(3):589-95.
11. Yoshihiko Chiba, Junko Arima, Hiroyasu Sakai, and Miwa Misawa. Am J Physiol Lung Cell Mol Physiol, 2008; 294: L705-L713.
12. V. Søyseth, P. H. Brekke, P. Smith, T. Omland Statin use is associated with reduced mortality in COPD. European Respiratory Journal 2007; 29: 279-283.
13. Stacey E. Alexeeff, Augusto A. Litonjua, David Sparrow, Pantel S. Vokonas and Joel Schwartz, V A Normative study. American Journal of Respiratory and Critical Care Medicine 2007; 176:742-747.
14. Blamoun AI, Batty GN, DeBari VA, Rashid AO, Sheikh M, Khan MA. Statins may reduce episodes of exacerbation and the requirement for intubation in patients with COPD: evidence from a retrospective cohort study. Int J Clin Pract. 2008 Sep; 62(9):1373-78.