

Efficacy and tolerability of atorvastatin as add on therapy in the treatment of chronic stable (moderate-severe) asthma for a duration of 8 weeks

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ABSTRACT

Atorvastatin, lipid lowering agent has a well established safety profile both in the primary and secondary prevention of cardiovascular diseases. Statins role as anti inflammatory and immunomodulatory effects what is called pleiotropism of statins is being explored and tried in the treatment of various diseases like asthma. Here this study highlights the efficacy and tolerability of atorvastatin as an add on therapy in the treatment of chronic stable asthma .this study concludes the statistical significance of atorvastatin 20mg dose as an adjuvant in chronic stable asthma.

Keywords: Atorvastatin, Chronic stable asthma, Immunomodulatory, Inflammatory, Pleiotropism

INTRODUCTION

Asthma is a problem worldwide with an estimated 300 million affected individuals. The prevalence of asthma ranges from 1% to 18% of population in different countries. The World Health Organization has estimated that 15 million disability adjusted life years (DALYs) are cost annually due to asthma, representing 1% of total global disease burden. The annual worldwide deaths from asthma have been estimated at 250,000.¹

Asthma is associated with inflammation of the airway wall. Increased number of various types of inflammatory cells, most notably eosinophils but also basophils, mast cells, macrophages, and certain types of lymphocytes, can be found in airway wall biopsies and bronchoalveolar lavage fluid from asthmatic patients.²

How bronchial inflammation contributes to asthmatic condition remains poorly understood. Although there are subtypes of asthma (allergic versus non allergic) there are

features of airway inflammation common to all asthmatic airways. The lymphocytes that participate in asthma pathology are biased toward the T-helper type 2 (Th2) phenotype, leading to an increase in production of interleukin 4 (IL-4), IL-5, and IL-13. The IL-4 from Th 2 cells (and basophils) provides help for IgE synthesis in B cells. The IL5 provides support for eosinophil survival. The chronic inflammatory response, over time, leads to epithelial shedding and reorganization, mucous hypersecretion, and airway wall remodeling most often exemplified by subepithelial fibrosis and smooth muscle hyperplasia.²

Statins reduce cholesterol levels by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMGCoA) reductase and have an established role in the treatment of atherosclerotic disease. Recent research has identified anti-inflammatory properties of statins. Statins appear to reduce the stability of lipid raft formation with subsequent effects on immune activation and regulation, and also inhibit signalling molecules with subsequent

downregulation of gene expression. Both these effects result in reduced cytokine, chemokine, and adhesion molecule expression with effects on cell apoptosis or proliferation.³

In allergic asthmatic models of mice, Simvastatin reduced ovalbumin-specific IgE level, the number of total inflammatory cells, including macrophages, neutrophils, and eosinophils into bronchoalveolar lavage fluid. In clinical studies, lung transplant recipients with statin therapy had a better survival rate than those without it. This result was probably reflected by down regulation of myofibroblast function with statin.³

The important key cell signalling molecule affected by statins appears to be Ras, which is a small guanosine triphosphate (GTP) –binding protein and is a key signalling molecule acting downstream of growth factors. Lovastatin can inhibit the activation of Ras through a modification of Ras localization to the inner plasma membrane of fibroblast.³

Moreover recent basic studies so called “bench” findings demonstrated that statins exhibit potent immunomodulation of the regulation of the T1/T2 polarization in animals or in vitro models.⁴

Keeping in mind the above evidences on the anti-inflammatory and immunomodulatory effects of statin, this study was taken up to evaluate 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, which was conducted at Chest Medicine out patient department, Government General Hospital, Chennai.

METHODS

Study Design

Open label, randomized, comparative, parallel group prospective study.

Study Centre

Department of Chest Medicine, Govt. General Hospital (GGH), Chennai.

Study Duration

8 weeks for each patient

Study Population

Patients attending Chest Medicine Out Patient Department, GGH, Chennai with chronic stable asthma (moderate-severe).

Study Sample

90 patients with 30 patients in each group

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

Group B: Standard therapy + Atorvastatin 10 mg

Group C: Standard therapy + Atorvastatin 20 mg

Inclusion Criteria

- Age 18 – 55 years
- Both genders
- Chronic moderate-severe asthma patients
 - -Symptoms of asthma (breathlessness, cough, wheezing chest tightness) for more than one year.
 - -Daily symptoms, daily use of bronchodilators, and or steroids with night or early morning symptoms more than once a week.
- Patients willing to give informed consent.

Exclusion Criteria

- Asthma exacerbations within 3 months necessitating increase in asthma medications.
 - Other respiratory infections, inflammatory disease, autoimmune disease.
 - Abnormal CPK, liver transaminases and renal diseases.
 - Patient already on statin therapy.
 - Unstable asthma
 - Previous statin sensitivity, myopathy or myositis
 - Diabetes mellitus
 - H/o chronic systemic illness
 - H/o coronary heart disease, hyperlipidemia, other conditions requiring statins
 - Those taking drugs known to cause interactions with Statins, like: macrolide, antibiotics, azole antifungals, digoxin, protease inhibitors etc.
 - Pregnant and lactating women

RESULTS

This study was taken up to assess the efficacy and tolerability of Atorvastatin in increasing doses as an add on therapy to standard therapy in reducing the frequency and exacerbations of symptoms of chronic stable asthma thereby decreasing the morbidity.

Out of 206 patients screened, 66 patients had hypercholesterolemia, 30 were smokers or ex-smokers, 10 were diabetic, 6 had exacerbations within 3 months needing hospitalization, 2 had elevated liver enzymes, 1 had elevated serum creatinine and 1 was a lactating woman. These patients were excluded from the study. 90 patients, who fulfilled the inclusion criteria, were recruited for the study. They were randomly allocated

into 3 groups (group A, B, C), each containing 30 patients by simple randomization method. Group A received standard treatment with Salbutamol 4 mg twice and Deriphylline 100 mg thrice daily. Group B, C received, in addition, Atorvastatin 10, 20 mg, once daily respectively. Each patient was under treatment for 8 weeks. Clinical, laboratory parameters including spirometry and asthma control score (subjective score) were done at baseline, 4 and 8 weeks. All the 90 patients completed the study.

Statistical analysis was done with one-way ANOVA and multiple comparisons with Bonferroni T test. Sex distribution was analysed with chi-square test.

Table 1: Mean duration of illness.

Groups	Mean duration of illness (in years)
Group A	16.06
Group B	15.33
Group C	15.26

Table 1 shows mean duration of illness was similar (statistically insignificant) in all the groups.

Figure 4 is the diagrammatic representation of the mean duration of illness among three groups.

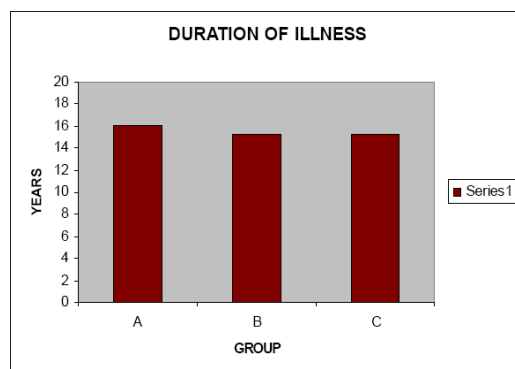


Figure 1: Mean duration of illness among groups.

Table 2

- At the baseline there was no statistical significance
- The ACS subjective score is significant after 4 and 8 weeks of study for group B and C.
- In between groups there was statistical significance between standard group A with group B and C.
- Also there was a statistical difference between group B and C suggesting that increase in Atorvastatin dose from 10 to 20 mg is beneficial in chronic asthmatics

Table 2: Comparison of ACS score.

Group	Baseline Mean±SD	After 4 weeks Mean±SD	After 8 weeks Mean±SD
Group A (N = 30) Standard Therapy	17.96±0.92	16.8±0.66	18.2±0.96
Group B (N = 30) Standard Therapy + Atorvastatin 10mg.	17.46±0.86	19.3±0.70	20.6±0.67
Group C (N = 30) Standard Therapy + Atorvastatin 20mg.	17.96±0.71	19.76±1.46	21.43±0.50
One way ANOVA	F=3.05 P=0.6 Not Significant	F=172.6 P=0.0001 Significant	F=155 P=0.0001 Significant
Bonferroni T-Test		AVsB, AVsC, BVsC P=0.0001	AVsB, AVsC, BVsC P=0.0001

Figure 2 is the diagrammatic representation of ACS score in all the study groups at baseline, 4 and 8 weeks.

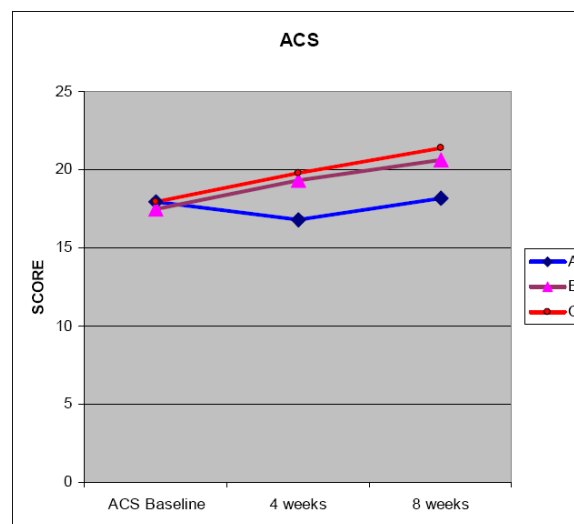


Figure 2: Comparison of ACS score.

Table 3 shows FEV₁ at baseline is not significant in all the groups.

FEV₁ at 8 weeks is statistically significant for group C (i.e. with a higher dose of Atorvastatin).

Table 3: Forced expiratory volume (1 second).

Group	FEV1 Baseline Mean±SD	FEV1 4 Weeks Mean±SD	FEV1 8 Weeks Mean±SD
Group A	127.53±59.14	127.4±53.9	136.1±56.72
Group B	107.36±54.13	126±57.9	141.4±58.9
Group C	114.17±45.79	151.6±53.7	188.16±63.49
One Way ANOVA F Test	F=1.11 P=0.33 Not Significant	F=2.05 P=0.12 Not Significant	F=6.89 P=0.001 Significant
Bonferroni T Test			A Vs B=0.24 A Vs C=0.007 B Vs C=0.51

There is a statistical significance in between group A and C which again shows that a higher dose of Atorvastatin is beneficial for asthmatics.

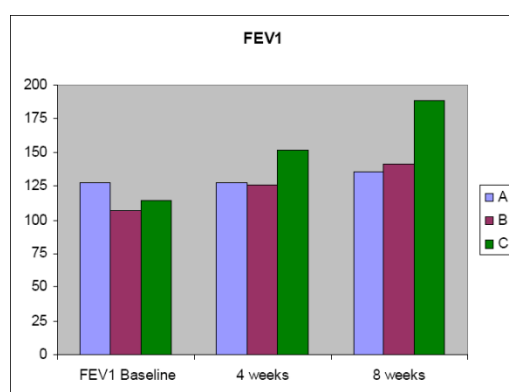


Figure 3: Forced expiratory volume (1 second).

Figure 3 is the diagrammatic representation of FEV₁ at baseline, 4 weeks and 8 weeks in all the groups.

Table 4: Peak expiratory flow.

Group	PEFR Baseline Mean±SD	PEFR 4 Weeks Mean±SD	PEFR 8 Weeks Mean±SD
Group A	158.6±81.4	154.76±75.1	170.23±78.37
Group B	149.63±108.58	191.46±128.21	220.7±131.73
Group C	134.4±76.2	203.63±99.65	260.33±115.7
One Way ANOVA F Test	F=0.56 P=0.6 Not Significant	F=1.82 P=0.168 Not Significant	F=4.98 P=0.009 Significant
Bonferroni T Test			A Vs B=0.24 A Vs C=0.007 B Vs C=0.51

Table 4 shows

- PEF at baseline is not significant in all the groups.

- PEF at 8 weeks is statistically significant in group C (i.e. with a higher dose of atorvastatin).
- There is a statistical significance between group A and C which shows that a higher dose of atorvastatin is beneficial for asthmatics.

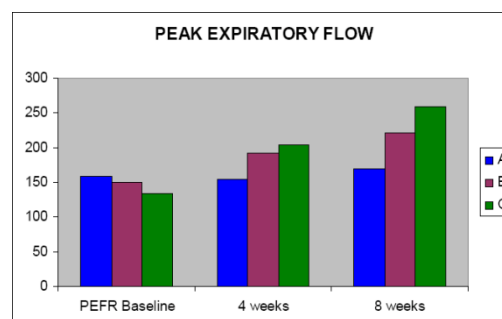


Figure 4: Peak expiratory flow.

Figure 4 is the diagrammatic representation of PEF at baseline, 4 and 8 weeks in all the groups

Table 5: Creatine phosphokinase (mg/dl).

Group	CPK Baseline Mean±SD	CPK 4 Weeks Mean±SD	CPK 8 Weeks Mean±SD
Group A	61±35.9	68.8±30.7	75.9±35.2
Group B	55±36	94±47.3	86.3±30.3
Group C	60±30.9	85.2±45.3	80.8±31.5
One Way ANOVA F Test	F=0.19 p=0.82 Not significant	F=2.87 p=0.063 Not significant	F=0.79 p=0.45 Not Significant

Table 5 shows mean creatine phosphokinase level is statistically insignificant at baseline, 4 and 8 weeks in all the groups.

Table 6 shows there is no statistical difference in mean serum creatinine between the three groups at baseline 4 and 8 weeks.

Table 6: Serum creatinine (mg/dl).

Group	Creatinine Baseline Mean±SD	Creatinine 4 Weeks Mean±SD	Creatinine 8 Weeks Mean±SD
Group A	1.13±0.18	1.13±0.18	1.13±0.18
Group B	1.14±0.16	1.14±0.16	1.12±0.16
Group C	1.07±0.19	1.07±0.19	1.09±0.18
One Way ANOVA F Test	F=1.19 p=0.309 Not significant	F=1.19 p=0.309 Not significant	F=0.46 p=0.631 Not Significant

Table 7 shows there is no statistical difference of mean SGPT in all the groups at baseline, 4 and 8 weeks.

Table 7: Serum glutamic pyruvate transaminase (SGPT).

Group	SGPT Baseline Mean±SD	SGPT 4 Weeks Mean±SD	SGPT 8 Weeks Mean±SD
Group A	38.5±3.7	41.3±6.16	44.7±7.6
Group B	37.36±4	41.53±6.2	43±7.8
Group C	37.86±3.98	40.86±6.2	43.1±7
One Way ANOVA F Test	F=0.63 p=0.53 Not significant	F=0.09 p=0.0913 Not significant	F=0.48 p=0.618 Not Significant

Table 8 shows there is no statistical difference of mean SGOT in all the groups at baseline, 4 and 8 weeks.

Table 8: Serum glutamic oxaloacetate transaminase (SGOT).

Group	SGOT Baseline Mean±SD	SGOT 4 Weeks Mean±SD	SGOT 8 Weeks Mean±SD
Group A	38.9±5.2	40.4±4.3	41.7±4.9
Group B	36.06±5.2	41.1±7.8	43.2±8.1
Group C	37.8±6.2	40.8±5.2	42.3±7.4
One Way ANOVA F Test	F=2 P=0.137 Not Significant	F=0.11p=0.89 Not Significant	F=0.38 P=0.683 Not Significant

Table 9 shows adverse events equally distributed among the three groups during the study period.

Table 9: Adverse Events.

Adverse Events	Group A	Group B	Group C
Myalgia	1	1	2
Nausea	1	1	1
Dyspepsia	2	2	1

Figure 5 is the diagrammatic representation of adverse events in the three groups during the study period.

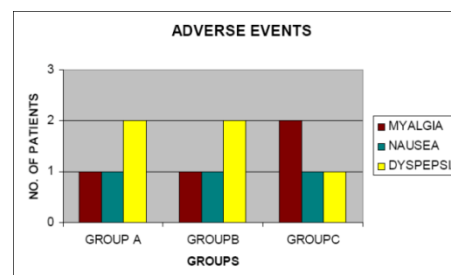


Figure 5: Adverse events.

DISCUSSION

Asthma is a chronic inflammatory disease of the lung characterized by episodic airway obstruction and increased bronchial responsiveness⁶. The concept that inflammation is a major component of asthmatic pathology was established more than 100 years ago by studies that used autopsy specimens to study the macroscopic, morphologic and histologic changes within the large asthmatic airways.⁷ It is now widely accepted that in asthmatics, recruitment of inflammatory cells, in particular eosinophils and T cells, also occurs in the distal lung^{8,9} and the lung parenchyma.¹⁰ At this distant site there are an abundance of T Helper -2 cytokines and chemokines,^{9,11} and pro inflammatory mediators including cyclo-oxygenase metabolites.¹² It is probable that any changes developing in the distal lung and in the parenchyma in patients who have asthma will have a dramatic effect on the pathogenesis and treatment of this disease.

Recent studies revealed an importance of a monomeric GTP-binding protein, RhoA, in contraction of bronchial smooth muscle (BSM). RhoA and its downstream have been proposed as a new target for the treatment of airway hyper responsiveness in asthma. Statins are known to inhibit the functional activation of RhoA via the depletion of geranylgeranylpyrophosphate.¹³

In the Normative Aging Study done at Boston, Massachusetts conducted with 803 elderly men whose lung function (FVC and FEV₁) was measured two to four times between 1995 and 2005, it was observed that, for those not using statins, the estimated decline in FEV₁ was 23.9 ml/year (95% confidence interval [CI], -27.8 to -20.1 ml/yr), whereas those taking statins had an estimated 10.9-ml/year decline in FEV₁ (95% CI, -16.9 to -5.0 ml/yr), which indicated that statin use attenuates decline in lung function in the elderly⁵.

In the study at discharge from a Norwegian teaching hospital, a retrospective cohort design with 854 consecutive patients (mean age 70.8 years, 51.5% female) with a diagnosis of COPD exacerbation were included. Median follow-up was 1.9 years, during which 333 patients died. The crude mortality rate per 1000 person-years was 110 in patients treated with statins, and 191 in patients not treated with statins. After adjustment for

gender, age, smoking, pulmonary function and comorbidities, the hazard ratio for statin users vs. statin non-users was 0.57 (95% confidence interval 0.38-0.87, $p=0.009$). Treatment with statins was associated with improved survival after COPD exacerbation.¹⁴

On the basis of the pleotropic effects of statins noted in the above studies, we conducted a study, in chronic stable asthmatics on standard therapy. Our study was a open label randomized comparative prospective parallel group study conducted in the Chest Medicine OPD, in Government General Hospital, Chennai. The patients were randomly allocated into 3 groups, and received their respective study medications.

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

Group B Standard therapy + atorvastatin 10 mg once daily

Group C Standard therapy + atorvastatin 20 mg once daily

The duration of the study was 8 weeks. They were evaluated every 4 weeks for symptomatic, spirometric and lab parameters. Data were compiled and the results were statistically analyzed.

Age: The average age among groups were 37-40 years with p value of 0.48 which is not significant among groups.

Sex: Among the 90 patients 68(75.56%) were females and 22(24.44%) were males. Statistical analysis showed no significant difference in the sex distribution between the groups.

Assessment of lung function

Spirometric readings were taken in all the patients at 0, 4 and 8 weeks. In our study there was statistically significant difference in values in patients taking atorvastatin 20mg (Group C). FEV₁ values increased significantly ($p=0.001$) at 8 weeks in group C. FEV₁ improvement in group C was 37.43ml at 4 weeks from baseline, 73.99ml at 8 weeks from baseline, as compared to group A, which had a decline of 0.13ml at 4 weeks from baseline, and only an increase of 8.57ml at 8 weeks from baseline. There was also a similar improvement in the PEF value in group C($p=0.009$). The other studies in atorvastatin had also showed a similar improvement in lung function.⁵

Lab parameters

There was statistical difference in ESR values in Group B and C patients with p values 0.003 and 0.001 respectively. This may indicate the anti-inflammatory effect of statin on asthmatic airways. The absolute

eosinophil count which is a marker of inflammation in chronic asthma has declined in group C patients as compared to group A patients ($p=0.05$).

Subjective score assessment

Asthma control score was used for subjective assessment. There was an increase in score in group B and C patients, suggesting the symptomatic improvement of asthma with statin, as compared to standard therapy alone.

A study conducted at St. Joseph's Regional Medical Center, in northern New Jersey (USA) assessed the rate of COPD exacerbations and intubations in patients receiving therapy with statins. The researchers conducted this comparative study(retrospective cohort) of 185 patients with COPD, hospitalized during one year.¹⁵ The results revealed that the average number of exacerbations among COPD patients not receiving statins was 1.59 per patient per year compared to 0.41 among patients on statin (odds ratio 13.83, 95% confidence 4.564 to 24.01; $p<0.001$) as measured by Mann Whitney test,¹⁵ where as in our study, the asthma symptom score measurements, there was a significant statistical difference in group B and C ($P=0.0001$) at 4 and 8 weeks.

Thus we noted that atorvastatin in increasing doses can be beneficial in chronic asthma by not only improving the lung function but also the symptoms.

Adverse events

There were no major adverse events noted during the study period. Lab parameters SGPT, SGOT, Urea, Creatinine, and CPK, all were within normal limits in all the groups studied. Minor self limiting adverse effects like myalgia, nausea and dyspepsia were equally distributed among the study groups which did not require drug discontinuation or any drugs to resolve the adverse effects. Thus, the safety of atorvastatin with increasing dose 10mg and 20mg in chronic stable asthma was determined in our study.

CONCLUSION

Based on the outcome of our study, we conclude that

- Atorvastatin, as an adjuvant is beneficial in the treatment of chronic stable asthma (moderate-severe).
- Higher doses of atorvastatin 20mg compared to 10mg once daily, as an add on therapy is more efficacious in the treatment of asthma.
- Atorvastatin in 10mg and 20mg is found to be safe in chronic stable asthmatics.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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