EFFICACY AND TOLERABILITY OF ATORVASTATIN AS AN ADD-ON THERAPY IN THE TREATMENT OF CHRONIC STABLE(MODERATE-SEVERE) ASTHMA

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CERTIFICATE

This is to certify that the dissertation entitled, **"*Efficacy and tolerability of Atorvastatin as an add on therapy in the treatment of chronic stable (moderate-severe) asthma*"** submitted by **Dr.N.Sunil,** in partial fulfillment for the award of the degree of Doctor of Medicine in Pharmacology by The Tamilnadu Dr.M.G.R. Medical University, Chennai is a bonafide record of the work done by him in the Institute of Pharmacology, Madras Medical College, during the academic year 2006 – 2009.

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CONTENTS

INTRODUCTION

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.

REVIEW OF LITERATURE

Review of literature

Asthma is defined as a chronic inflammatory disease of airways that is characterized by increased responsiveness of the tracheobronchial tree to a multiplicity of stimuli . It is manifested physiologically by a widespread narrowing of the air passages, which may be relieved spontaneously or as a result of therapy, and clinically by paroxysms of dyspnoea, cough, and wheezing. Asthma is an episodic disease, with acute exacerbations interspersed with symptom-free periods. Typically, most attacks are short-lived, lasting minutes to hours, and clinically the patient seems to recover completely after an attack. However, there can be a phase in which the patient experiences some degree of airway obstruction daily.[4]

History of asthma[5]:

The actual term asthma is a Greek word that is derived from the verb aazein, meaning to exhale with open mouth, to pant. The expression asthma appeared for the first time in the Iliad, with the meaning of a short-drawn breath, but the earliest text where the word is found as a medical term is the Corpus Hippocraticum. The best clinical description of asthma in later antiquity is offered by the master clinician, Aretaeus of Cappadocia (1st century A.D.). The numerous mentions of "asthma" in the extensive writings of Galen (130-200 A.D.) appear to be in general agreement with the Hippocratic texts and to some extent with the statements of Aretaeus.

Moses Maimonides, a renowed 12th century rabbi, philosopher, and physician practiced in the court of Saladin (1137-1193), sultan of Egypt and Syria. Maimonides wrote a treatise on asthma for his royal patient, Prince Al-Afdal.

Jean Baptiste Van Helmont, a Belgium physician during the 16th century, wrote that asthma originated in the pipes of the lungs. In the 17th century, Bernardino Ramazzini, a Italian physician, noted a connection between asthma and organic dust.

Asthma was first described in the medical literature in the mid-1800's and still considered rare at that time. Found in Egypt in the 1870s, the Georg Ebers Papyrus contains prescriptions written in hieroglyphics for over seven hundred remedies

The use of bronchodilators started in 1901. It was not until the 1960s that the inflammatory component of asthma was recognized, and anti-inflammatory medications were added to the regimen.[5]

Epidemiology :

· Asthma is a common disease, affecting approximately 5% of the population.[6] Bronchial asthma occurs at all ages but predominantly in early life. About one-half of cases develop before age 10, and another third occur before age 40. In childhood, there is a 2:1 male/female preponderance, but the sex ratio equalizes by age 30. [4]

Etiology :

Genetics

More than 22 loci on 15 autosomal chromosomes have been linked to asthma. Although the genetic linkage to asthma has sometimes differed between cohorts, asthma has been consistently linked with loci containing pro allergic, pro inflammatory genes (IL4 gene cluster on chromosome 5). Genetic variation in receptors for different asthma medications is associated with variation in biologic response to these medications(polymorphisms in beta-2 adrenergic receptor) .other candidate genes include ADAM-33,(member of metalloproteinase family), the gene for the prostanoid DP receptor, and genes located on chromosome 5q 31(possibly IL12).[7]

Environment [6]

Common aeroallergens include house dust mites (often found in pillows, mattresses, upholstered furniture, carpets, and drapes), cockroaches, cats, and seasonal pollens.

Exposure to environmental tobacco smoke increases asthma symptoms and the need for medications and reduces lung function. Increased air levels of respirable particles, ozone, SO_2, and NO_2 precipitate asthma symptoms and increase emergency department visits and hospitalizations.

Pathogenesis :

The most popular hypothesis at present for the pathogenesis of asthma is that it derives from a state of persistent sub acute inflammation of the airways. An active inflammatory process is frequently observed in endobronchial biopsy specimens even from asymptomatic patients.[8]

The cells thought to play important parts in the inflammatory response are mast cells, eosinophils, lymphocytes, and epithelial cells. The roles of neutrophils and macrophages are less well defined. Each of these cell types can contribute mediators and cytokines to initiate and amplify both acute inflammation and the long-term pathologic changes described above. [8]

The mediators released histamine; bradykinin; the leukotrienes C, D, and E; platelet-activating factor; and prostaglandins (PGs) E2, F2alpha, and D2 produce an intense, immediate inflammatory reaction involving bronchoconstriction, vascular congestion, and edema formation. In addition to their ability to evoke prolonged contraction of airway smooth muscle and mucosal edema, the leukotrienes may also account for some of the other pathophysiologic features of asthma, such as increased mucus production and impaired mucociliary transport. This intense local event can then be followed by a more chronic one. The chemotactic factors elaborated (eosinophil and neutrophil chemotactic factors of anaphylaxis and leukotriene B4) bring eosinophils, platelets, and polymorphonuclear

leukocytes to the site of the reaction. These infiltrating cells as well as resident macrophages and the airway epithelium itself potentially are an additional source of mediators to enhance both the immediate and the cellular phase.[8]

The airway epithelium is both the target of, and a contributor to, the inflammatory cascade. These cells amplify bronchoconstriction by elaborating endothelin-1 and promoting vasodilatation through the release of nitric oxide, PGE2 and the 15-hydroxyeicosatetraenoic acid (15-HETE) products of arachidonic acid metabolism. They also generate cytokines such as granulocyte-macrophage colony stimulating factor (GM-CSF), interleukin (IL)8, Rantes, and eotaxin.[8]

Like the mast cell in the early reaction, the eosinophil appears to play an important part in the infiltrative component. The granular proteins in this cell (major basic protein and eosinophilic cationic protein) and oxygen-derived free radical are capable of destroying the airway epithelium, which then is sloughed into the bronchial lumen in the form of Creola bodies. Besides resulting in a loss of barrier and secretory function, such damage elicits the production of chemotactic cytokines, leading to further inflammation.[8]

T lymphocytes also appear to be important in the inflammatory response. These cells are present in increased numbers in asthmatic airways and produce cytokines that activate cell-mediated immunity, as well as humoral (IgE) immune responses. Activated T cells recovered from the

lungs of persons with asthma express messenger RNA for the cytokines known to play a part in the recruitment and activation of mast cells and eosinophils.[8]

Furthermore, the Th1 and Th2 lymphocyte subtypes have functions that may influence the asthmatic response. The Th1 cytokines IL-2 and interferon (IFN) gamma can promote the growth and differentiation of B cells and the activation of macrophages, respectively. The Th2 cytokines IL-4 and IL-5 stimulate B-cell growth and immunoglobulin secretion, and IL-5 promotes eosinophil proliferation, differentiation, and activation. It can also facilitate granule release from basophils.[4]

T-helper cell type Th2 lymphocytes play an important role in the initiation, progression and persistence of allergic diseases, including asthma. However, little is known about immunoregulatory mechanisms that determine susceptibility to, severity of, or persistence of asthma.[8]

Cytokines are synthesized and released from many of the inflammatory cells mentioned above, as well as from epithelial cells, fibroblasts, endothelial cells, and airway smooth muscle. Cytokines activate specific cell-surface receptors that are coupled to signal transduction pathways, which often result in alterations of gene regulation and enzyme production. The cytokines that are particularly relevant to asthma are secreted by T lymphocytes and include IL-3 (enhanced mast cell survival), IL-4 and IL-13 (switching of B lymphocytes to IgE production and expression of adhesion molecules), and IL-5 (differentiation and enhanced survival of eosinophils).

Other cytokines, such as IL-1B, IL-6, IL-11, tumor necrosis factor alfa (TNF-α) and GM-CSF, are proinflammatory and may amplify the inflammatory response. [4]

Clinical features:

ESSENTIALS OF DIAGNOSIS [6]

- Episodic or chronic symptoms of airflow obstruction: breathlessness, cough, wheezing, and chest tightness.
- Symptoms frequently worse at night or in the early morning.
- Prolonged expiration and diffuse wheezes on physical examination.
- Limitation of airflow on pulmonary function testing or positive bronchoprovocation challenge.
- Complete or partial reversibility of airflow obstruction, either spontaneously or following bronchodilator therapy.

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Classification of Asthma Severity by Clinical Features Before Treatment [6]

Intermittent

- Symptoms less than once a week
- Brief exacerbations
- Nocturnal symptoms not more than twice a month
- FEV1 or PEF= 80% predicted
- PEF or FEV1 variability < 20%

Mild Persistent

- Symptoms more than once a week but less than once a day
- Exacerbations may affect activity and sleep
- Nocturnal symptoms more than twice a month
- FEV1 or PEF = 80% predicted
- PEF or FEV1 variability < 20 -30%

Moderate Persistent

- Symptoms daily
- Exacerbations may affect activity and sleep
- Nocturnal symptoms more than once a week
- Daily use of inhaled short-acting Beta-2-agonist
- FEV1 or PEF 60-80% predicted
- PEF or FEV1 variability > 30%

Severe Persistent

- Symptoms daily
- Frequent exacerbations
- Frequent nocturnal asthma symptoms
- Limitation of physical activities
- FEV1 or PEF = 60% predicted
- PEF or FEV1 variability > 30%

DIAGNOSIS

CLINICAL DIAGNOSIS

Medical History

Symptoms - A clinical diagnosis of asthma is often prompted by symptoms such as episodic breathlessness, wheezing, cough, and chest tightness. Episodic symptoms after an incidental allergen exposure, seasonal variability of symptoms and a positive family history of asthma and atopic disease are also helpful diagnostic guides. The patterns of these symptoms that strongly suggest an asthma diagnosis are variability; precipitation by non-specific irritants, such as smoke, fumes, strong smells, or exercise; worsening at night; and responding to appropriate asthma therapy.[6]

Measurements of lung function.

Spirometry and measurement of lung volumes allow measurement of the presence and severity of obstructive and restrictive pulmonary dysfunction. Obstructive dysfunction is marked by a reduction in airflow rates judged by a fall in the ratio of FEV_1 (forced expiratory volume in the first second) to FVC (forced vital capacity). Causes include asthma, COPD (chronic bronchitis and emphysema), bronchiectasis, bronchiolitis, and upper airway obstruction.[6]

Since office spirometry is inexpensive and easy to perform there seems to be little justification for sacrificing diagnostic sensitivity and specificity by using peak flow measurements made in the office [9]

Radiography

Chest radiographs are generally unremarkable in patients with uncomplicated asthma. It is used primarily to exclude other causes of respiratory symptoms. Nonspecific radiographic findings, such as over inflation and prominent hilar vessels, have been reported in upto 31% of patients between the ages of 15 and 65 years who first developed asthmatic symptoms before age 15 years.[10]

Electrocardiogram

Asthma in remission is usually not associated with electrocardiographic abnormalities. During an acute exacerbation, however, several abnormalities can occur, including sinus tachycardia, P- pulmonale, right axis deviation, right bundle branch block, right ventricular strain, repolarization abnormalities, and variety of arrhythmias.[11]

Eosinophil count

Peripheral blood eosinophilia (greater than 4% or 300 to 400 per mm^3) may be seen in both allergic and non allergic asthmatics. When present, eosinophilia may be used to support a diagnosis of asthma; however, its absence is of no value in excluding asthma. It should be noted that eosinophilia may not be present if the patient is taking corticosteroids.[11]

Eosinophil counts have been shown to correlate with peak flow measurements in asthmatics whose disease is poorly controlled. Eosinophil cationic protein, eosinophil granule protein, has also been shown to

correlate with peak flow and is thought to reflect not only eosinophil numbers but eosinophil activity as well.[12]

Nitric oxide levels

Mixed expired concentrations of nitric oxide have been shown to fall during glucocorticoid therapy in patients with severe exacerbations of asthma, suggesting a possible role for nitric oxide as an index of disease severity or treatment efficacy.[13]

Management of asthma

Nonpharmacological therapy

Although pharmacological therapy has been an unexpendable component of good asthma management, nonpharmacological management strategies, including patient education and avoidance of asthma triggers are also important. Recent studies suggest that patient education and environmental control programs are effective in reducing asthma morbidity.[14]

Education

Controlled trials evaluating structured education and self management programs result in better asthma control and decreased emergency room visits and hospitalizations.[15,16] An understanding that asthma is a chronic disorder that is unlikely ever to go into complete remission is of primary importance. Instructions in the proper use of inhaled medications are of importance: so too is the description of likely triggers of episodes of asthma and ways to avoid such triggers. Finally

teaching the patient to recognize and intervene in exacerbations in the earliest stages can be helpful in avoiding more serious morbidity and in some cases mortality.[14]

Environmental control

Avoidance of aeroallergens, viral respiratory pathogens, air pollution, and certain drugs (beta blockers, aspirin etc.) can prevent exacerbations, reduce the need for drug treatment, and decrease utilization of emergency facilities.[14] Complete removal from exposure of house dust mites has been shown to reduce asthma severity and to reduce airway hyperresponsivenes.[17]

Pharmacological therapy [4]

The available agents for treating asthma can be divided into two general categories: drugs that inhibit smooth muscle contraction, i.e., the so-called "quick relief medications" (beta-adrenergic agonists, methylxanthines, and anticholinergics) and agents that prevent and/or reverse inflammation, i.e., the "long-term control medications" (glucocorticoids, leukotriene inhibitors and receptor antagonists, and mast cell-stabilizing agents).

Adrenergic Stimulants

The drugs in this category consist of the catecholamines, resorcinols, and saligenins. These agents are analogues and produce airway dilation through stimulation of beta -adrenergic receptors. They also decrease release of mediators and improve mucociliary transport. The

catecholamines available for clinical use are epinephrine, isoproterenol, and isoetharine. As a group, these compounds are short-acting (30 to 90 min) and are effective only when administered by inhalational or parenteral routes. Epinephrine also has substantial alpha-stimulating effects. The usual dose is 0.3 to 0.5 mL of a 1:1000 solution administered subcutaneously. Isoproterenol is devoid of alpha activity and is the most potent agent of this group. It is usually administered in a 1:200 solution by inhalation. Isoetharine, a β_2-selective compound of this class is a relatively weak bronchodilator. It is employed as an aerosol and supplied as a 1% solution. The use of these agents in treating asthma has been superceded by longer acting selective β_2 agonists.[4]

The commonly used resorcinols are metaproterenol, terbutaline, and fenoterol, and the most widely known saligenin is albuterol (salbutamol). With the exception of metaproterenol, these drugs are highly selective for the respiratory tract and virtually devoid of significant cardiac effects except at high doses. Their major side effect is tremor. They are active by all routes of administration, and because their chemical structures allow them to bypass the metabolic processes used to degrade the catecholamines, their effects are relatively long-lasting (4 to 6 h). Differences in potency and duration among agents can be eliminated by adjusting doses and/or administration schedules.[4]

Inhalation is the preferred route of administration because it allows maximal bronchodilation with fewer side effects. Salmeterol is a

very long-lasting (9 to 12 h) congener of albuterol. When given every 12 h, it is effective in providing sustained symptomatic relief. It is particularly helpful for conditions such as nocturnal and exercise-induced asthma. It is not recommended for the treatment of acute episodes because of its relatively slow onset of action (approximately 30 min), nor is it intended as a rescue drug for breakthrough symptoms. In addition, its long half-life means that administration of extra doses can cause cumulative side effects.[4]

Methylxanthines

Theophylline and its various salts are medium-potency bronchodilators that work by increasing cyclic AMP by the inhibition of phosphodiesterase. The therapeutic plasma concentrations of theophylline traditionally have been thought to lie between 10 and 20 ug/mL. Theophylline clearance, and thus the dosage requirement, is decreased substantially in neonates and the elderly and those with acute and chronic hepatic dysfunction, cardiac decompensation, and cor pulmonale. Clearance is also decreased during febrile illnesses. Clearance is increased in children. In addition, a number of important drug interactions can alter theophylline metabolism.[4]

For maintenance therapy, long-acting theophylline compounds are available and are usually given once or twice daily. The dose is adjusted on the basis of the clinical response with the aid of serum theophylline measurements. Single-dose administration in the evening reduces nocturnal symptoms and helps keep the patient complaint-free during the day. Aminophylline and theophylline

are available for intravenous use. The most common side effects of theophylline are nervousness, nausea, vomiting, anorexia, and headache. At plasma levels greater than 30 ug/mL there is a risk of seizures and cardiac arrhythmias.[4]

Anticholinergics

Anticholinergic drugs such as atropine sulfate produce bronchodilation in patients with asthma, but their use is limited by systemic side effects. Non absorbable quaternary ammonium congeners(atropine methylnitrate and ipratropium bromide) have been found to be both effective and free of untoward effects.[4]

Glucocorticoids

Glucocorticoids are the most potent and most effective anti-inflammatory medications available. Systemic or oral steroids are most beneficial in acute illness when severe airway obstruction is not resolving or is worsening despite intense optimal bronchodilator therapy, and in chronic disease when there has been failure of a previously optimal regimen with frequent recurrences of symptoms of increasing severity. Inhaled glucocorticoids are used in the long-term control of asthma. These drugs are indicated in patients with persistent symptoms.[4]

There is no fixed dose of inhaled steroid that works for all patients. Requirements are dictated by the response of the individual and wax and wane in concert with progression of the disease. In addition to thrush and dysphonia, the increased systemic absorption that accompanies larger doses of inhaled steroids has been reported to produce adrenal suppression, cataract formation,

decreased growth in children, interference with bone metabolism, and purpura. As is the case with oral agents, suppression of inflammation, per se, cannot be relied upon to provide optimal results [4]

Mast Cell-Stabilizing Agents

Cromolyn sodium and nedocromil sodium do not influence airway tone. Their major therapeutic effect is to inhibit the degranulation of mast cells, thereby preventing the release of the chemical mediators of anaphylaxis. Cromolyn sodium and nedocromil, like the inhaled steroids, improve lung function; reduce symptoms, and lower airway reactivity in persons with asthma. They are most effective in atopic patients who have either seasonal disease or perennial airway stimulation. A therapeutic trial of two puffs four times daily for 4 to 6 weeks frequently is necessary before the beneficial effects of the drug appear. Unlike steroids, nedocromil and cromolyn sodium, when given prophylactically, block the acute obstructive effects of exposure to antigen, industrial chemicals, exercise, or cold air. With antigen, the late response is also abolished. [4]

Leukotriene Modifiers

As mentioned earlier, the cysteinyl leukotrienes (LTC4, LTD4, and LTE4) produce many of the critical elements of asthma, and drugs have been developed to either reduce the synthesis of all of the leukotrienes by inhibiting 5-lipoxygenase (5-LO), the enzyme involved in their production, or competitively antagonizing the principal moiety (LTD4). Zileuton is the only 5-lipoxygenase synthesis inhibitor that is available in the United States. It is a modest

bronchodilator that reduces asthma morbidity, provides protection against exercise-induced asthma, and diminishes nocturnal symptoms, but it has limited effectiveness against allergens. Hepatic enzyme levels can be elevated after its use, and there are significant interactions with other drugs metabolized in the liver. The LTD4 receptor antagonists (zafirlukast and montelukast) have therapeutic and toxicologic profiles similar to that of zileuton but are long acting and permit twice to single daily dose schedules.[4]

Miscellaneous Agents

It has been suggested that steroid-dependent patients might benefit from the use of immunosuppressant agents such as methotrexate or gold salts. The effects of these agents on steroid dosage and disease activity are minor, and side effects can be considerable. Consequently, this form of treatment can be viewed only as experimental.[4]

Bronchial thermoplasty (BT)[18]

Bronchial thermoplasty (BT) reduces the potential for smooth muscle–mediated bronchoconstriction by reducing the mass of smooth muscle in the walls of conducting airways [18].

Biological therapies for treatment of asthma

A major goal of translational research in asthma is to elucidate the immune mechanisms involved in this disease and to develop biologic agents, specifically engineered proteins that alter immunologic events in its pathogenesis.[19]

B cell/ Ig E Blockade(Omalizumab)

Omalizumab was administered in subcutaneous dose based on serum total IgE level and body weight which was 0.016mg/kg/IgE (IU/ml)/month divided every 2 to 4 weeks , a reduction in inhaled corticosteroids dose of 50% or more was seen in 72.4%[20] and 80.4%[21] of Omalizumab treated patients as compared with 54.9%[20]or 66.9%[21] of the placebo treated patients .The main limitation to the use of Omalizumab is its high cost.

T cell manipulation

Asthma can be distinguished from other chronic inflammatory diseases such as rheumatoid arthritis , crohns disease, and psoriasis in that it is dominated by Th 2 cytokines mainly IL-4 IL-5, IL-9 and IL-13 all of which cluster on chromosome 5q.[22]

It has been suggested that polarization of the immune response toward a Th 2- dominated disease such as asthma results from the reduction in the influence of Th 1 cytokines especially IL-18, IL-12, and Interferon –gamma.[23] Weirenga and colleagues[24] showed that allergen- specific T cells from nonallergic individuals convert a Th 2 to a Th 1 cytokine profile.

Biological therapies under clinical trial

Altrakincept (soluble rebombinant IL-4 receptor)in two large phase 3 clinical trials fail to show clinical efficacy.[22]

Pascolizumab is a humanized anti IL-4 monoclonal antibody (IgG1) that blocks the interaction of IL-4 with its receptor and inhibits the early events of chronic asthma.[24]

Interferon gamma [25,26,27], IL-10[28] ,IL-12 [29] have therapeutic promise in altering the Th 1/Th 2 balance in asthmatic patients.

Some researchers have observed that anti- TNF therapy improved control of both asthma and rheumatoid arthritis.[30]

Modulation of cell trafficking

Efalizumab approved for use in patients with psoriasis , is a humanized Ig G1 monoclonal antibody against the LFA-1 alpha chain,(CD11a).[31]

Intracellular targets

Transcription factors

Nuclear Smad proteins are a family of transcription factors to which transforming growth factor-beta signals are transduced, there by mediating its inflammatory effects in asthmatic airway: Nuclear Smad proteins too may targets for novel therapeutic strategies for asthma.[32]

Protein kinases

Blockade of p38 MAP (mitogen activated protein)-Kinase with the novel cytokine suppressant anti inflammatory drugs (CSAIDS) has been shown to inhibit the synthesis of Th2 cytokines preferentially[33]and to decrease eosinophil survival [34].Phase 2 development of these inhibitors is underway.[35]

STATINS:

These drugs are competitive inhibitors of 3-hydroxy-3-methylglutaryl co enzyme A (HMGCoA) reductase, which catalyzes an early, rate limiting step in cholesterol biosynthesis. Alberts and colleagues at Merck developed the first

statin approved for use in humans, Lovastatin (formerly known as mevinolin), which was isolated from Aspergillus Terreus. Five other statins are also available. Pravastatin and Simvastatin are chemically modified derivatives of Lovastatin, Atorvastatin, Fluvastatin and Rosuvastatin are structurally distinct synthetic compounds.[36]

Mechanism of action:[36]

Statins exert their major effect-reduction of LDL levels through a mevalonic acid-like moiety that competitively inhibits HMGCoA reductase.

Kinetics:

All have high first pass metabolism by the liver. Most of the absorbed dose is excreted in the bile.5-20% is excreted in the urine. Plasma half –lives of these drugs range from 1 hour to 3 hours except for Atorvastatin, which has a half life of 14 hours and rosuvastatin,19 hours. The catabolism of Lovastatin, Simvastatin and Atorvastatin proceeds chiefly through CYP3A4, whereas that of Fluvastatin and Rosuvastatin is mediated by CYP2C9.[37]

Pharmacodynamics:

Action of statins on LDL levels:

Statins affect blood cholesterol levels by inhibiting hepatic cholesterol synthesis, which results in increased expression of the LDL receptor gene.

Some studies suggest that statins can also reduce LDL levels by enhancing the removal of LDL precursors and by decreasing hepatic VLDL production.[36]

Action on Triglycerides:

Triglyceride levels >250 mg/dl. are reduced substantially by statins,and the percent reduction achieved is similar to the percent reduction in LDL-C. [36]

Effect on HDL-C level:

In studies of patients with elevated LDL-C levels and gender appropriate HDL-C levels (40 to 50mg/dl for men; 50 to 60 mg/dl for women) an increase in HDL-C of 5 to 10% was observed irrespective of the dose of statin employed.[36]

Pleiotropic effects of statins:

Because mevalonate, the product of the enzyme reaction, is the precursor not only of cholesterol, but also of many nonsteroidal isoprenoid compounds, inhibition of HMG CO A reductase may produce pleiotropic effects.[38] Pleiotropic effects are defined as producing or having multiple effects from a single gene.[39]

Pleiotropic effects of statins: [40]

- Improved endothelial function
- Reduced vascular inflammation
- Reduced platelet aggregability
- Increased neovascularisation of ischemic tissue
- Increased circulating endothelial progenitor cells
- Stabilization of atherosclerotic plaque
- Antithrombotic actions
- Enhanced fibrinolysis

- ❖ Osteoclast apoptosis and increased synthetic activity in osteoblasts
- ❖ Inhibition of germ cell migration during development
- ❖ Immune suppression.

Dosage:

Atorvastatin,10-80mg/d;Fluvastatin,20-40mg/d; Lovastatin,10- 80mg/d; Pravastatin, 10- 40mg/d; Rosuvastatin,5-40mg/d; and Simvastatin 5-40mg/d.[36]

The hepatic cholesterol synthesis is maximal between midnight and 2.00 AM. Thus statins with half-lives of 4 hours or less (all but Atorvastatin and Rosuvastatin) should be taken in the evening.[36]

Therapeutic indications of statins: [41]

- A series of clinical trials has demonstrated the efficacy of HMGCoA reductase inhibitors in preventing death, coronary events and strokes.
- Beneficial results have been found in patients who have already experienced coronary events (secondary prevention) in those particularly at high risk for events (diabetics and patients with peripheral artery disease and those with elevated LDL-C without multiple risk factors).
- There is now clear evidence that treatment with statins can prevent coronary events and stroke in patients without clinical manifestation of atherosclerosis (primary prevention) and LDL levels as low as 130 mg/dl.
- The PROVE –IT trial provides evidence for starting a statin in the days

immediately following an acute coronary syndrome. In this trial, more intensive therapy with Atorvastatin 80mg a day, regardless of total or LDL cholesterol, improved outcome compared to Pravastatin 40 mg a day, with the curves of death or major cardiovascular event separating as early as 3 months after starting therapy.

- The Heart Protection study demonstrated that Simvastatin 40 mg daily reduces vascular events by more than 20% in patients' prior myocardial infarction, stroke, peripheral vascular disease, or diabetes with total cholesterol levels as low as 135 mg/dl. The treatment benefit was similar regardless of baseline LDL cholesterol, with equal benefit above or below 100mg/dl.This result suggests that all patients at significant risk for vascular events should receive statin regardless of their cholesterol levels.

ADR: HMG-co A reductase inhibitors are well tolerated. Mild unwanted effects include gasterointestinal disturbances, increased plasma concentration of liver enzymes, insomnia and rash. More severe adverse effects are rare but include severe myositis and rhabdomyolysis and angioedema.[40]

Myopathy: [36] The incidence of myopathy is quite low (~0.01).Factors inhibiting statin catabolism are associated with increased myopathy risk, including

- advanced age(especially more than 80 years of age),
- hepatic or renal dysfunction,
- perioperative periods
- multisystem disease(especially in association with diabetes mellitus small body size, and untreated hypothyroidism).

- Concomitant use of drugs that diminish statin catabolism is associated with myopathy and rhabdomyolysis in 50%to 60% of cases.

The most common statin interactions occurred with Fibrates; especially Gemfibrozil 38%, Cyclosporine 4%, Digoxin 5%, Warfarin 4%, Macrolide antibiotics 3%, Mibefradil 2% and Azole antifungals 1%.Other drugs that increase the risk of statin induced myopathy include niacin, HIV protease inhibitors, Amiodarone and Nefazodone.

The clinical presentation of myopathy: [42]

- ❖ Lower extremity pain
- ❖ Weakness associated with stair climbing
- ❖ Inability to open jars
- ❖ Proximal weakness of the shoulder, hip and knee musculature and
- ❖ Severe muscle cramps

In addition to myalgic complaints, patients with HMGRI-related myopathy may have CPK activity values more than 10 times the upper limit of normal for a given reference laboratory (>2200 U/L for males and >1500 U/L for females).[42]

Rhabdomyolysis: It is a serious muscle damage with CPK levels more than 10 times upper limit of normal. Rhabdomyolysis results in the release of myoglobin into the blood stream, causing possible damage to the kidneys and other organs.[43] **Symptoms-** generalized or specific myalgia, muscle tenderness, fever, nausea, vomiting and dark urine.[42] **Incidence of rhabdomyolysis:** < 1 death per million prescriptions for all statins, except Cerivastatin, which had an

incidence of >3 deaths per 1 million prescriptions and withdrawn from the market.[44]

Mechanism for the adverse effects on muscle:[43]

Figure :1

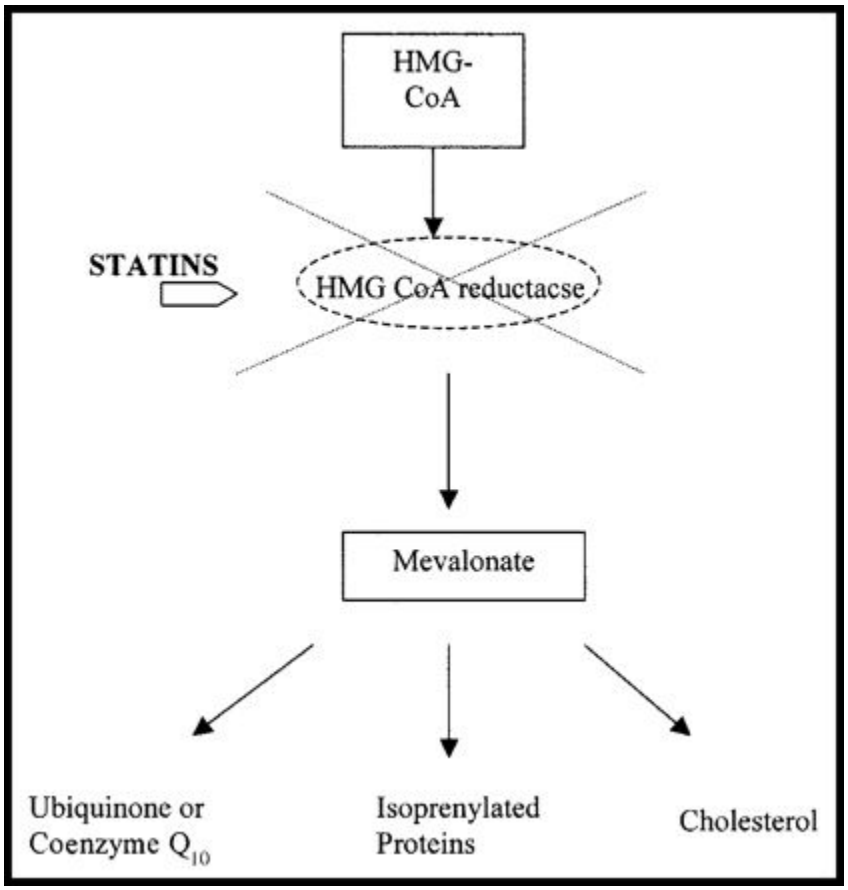


Figure 1 shows the mechanism of action and adverse effect of statins.

Because statins inhibit the production of mevalonate, a precursor of Co Q_{10} the synthesis of CoQ_{10} also may be inhibited.[42] Because Co Q_{10} is involved in energy production via the mitochondrial respiratory chain, a decrease in $Co.Q_{10}$ explain some adverse muscle effects.[44]There is some evidence to indicate that statin use can exacerbate the normal CPK elevations seen after exercise.[45]Since myopathy rarely occurs in the absence of

combination therapy, routine CPK monitoring is not recommended unless statins are used with one of the predisposing drugs.[36]

Trials using statins as anti inflammatory and immunomodulatory agent:

Atorvastatin and Simvastatin have been shown to reduce CRP levels in a small study of 66 hyperlipidemic patients with coronary artery disease.[46]

- Evaluation of recent clinical trials, including WOSCOPS, PRINCE, AFCAPS / TexCAPS, MIRACL, REVERSAL, and JUPITER, demonstrated the correlation of statin therapy with decreased levels of CRP. WOSCOPS found that patients with CRP values of > 4.59mg/l at baseline were at the highest risk of coronary events. MIRACL showed that Atorvastatin reduced CRP levels by 83 %($p < 0.001$). Results of the REVERSAL study linked Atorvastatin with a 36.4% decrease in CRP levels.[47]
- Many in vitro and animal studies now describe the potential anti inflammatory effects of statins. After exposure to statins, endothelial cells exhibit increased endothelial nitric oxide synthase and tissue plasminogen activator antigen with reduced plasminogen inhibitor 1, tissue factor, and endothelin expression.[48]
- Macrophage chemokine release, chemotactic responses and oxidative burst are reduced by statins, as is NK cell cytotoxicity in vitro. Antineutrophil cytoplasmic antibody induced neutrophil activation is also suppressed in vitro.[49] Together these effects suggest that innate immune

responses may be susceptible to inhibition of HMG-CO A reductase. Similarly, effects on acquired immune responses have emerged. Statins suppress antigen presenting cell major histocompatability complex-II expression, Tcell-macrophage interactions through leukocyte function antigen-1/.intercellular adhesion molecule-1(LFA-1/ICAM-1),Tcell proliferation and interferon ɣ release, and modify polarization of Th1 responses in vitro and in vivo rodent model. In vivo suppressive effects by various statin moieties have been described in rodent experimental allergic encephalomyelitis, carrageenan induced inflammation, renal ischemia reperfusion injury and transplant models.[48]

ATORVASTATIN [36]

- Synthetic compound.
- Uptake is mediated by the organic anion transporter 2(OAPT 2)
- Half life about 20 hours
- Metabolized by CYP3A4
- The starting dose is 10mg and the maximum is 80 mg.
- Indicated for children age 8 or older
- The safety of statins during pregnancy has not been established.

In large trials involving patients with hypercholesterolemia Atorvastatin produced greater reductions in total cholesterol, LDL-C, apolipoprotein B and TGL levels than lovastatin, Pravastatin and Simvastatin. In comparative trials, Atorvastatin had a similar adverse event profile to that of other

HMGCoA reductase inhibitors.[50]This pronounced effect of Atorvastatin seems to be due to its long-lasting action, presumably a reflection of longer residence time of Atorvastatin and its active metabolites in the liver.[51]Atorvastatin reduces LDL-C dependently across 10-80 mg. dose range (35.7%-52.2%).[52] Until recently, atorvastatin was known only as a but more potent statin (' me too' drug) for lowering LDL- C. In the last 2 years data has become available on nearly 32,000 patients, in clinical settings ranging from primary prevention to acute coronary syndromes.[53]

Preclinical study of statins in asthma [54]

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 hyperresponsiveness in asthma. Statins are known to inhibit the functional activation of RhoA via the depletion of geranylgeranylpyrophosphate.

Rats were sensitized and repeatedly challenged with 2,4-dinitrophenylated *Ascaris suum* antigen. Animals were also treated with Lovastatin (4mg/kg/day ip) once a day before and during the antigen inhalation period. Repeated antigen inhalation caused a marked BSM hyperresponsiveness to ACh with the increased expression and translocation of RhoA. Lovastatin treatments significantly attenuated both the augmented contraction and RhoA translocation to the plasma membrane.

Lovastatin also reduced the increased cell number in bronchoalveolar lavage fluids and histological changes induced by antigen

exposure, whereas the levels of immunoglobulin E in sera and interleukins 4, 6, and 13 in bronchoalveolar lavage fluids were not significantly changed. These findings suggest that Lovastatin ameliorates antigen-induced BSM hyperresponsiveness, an important factor of airway hyperresponsiveness in allergic asthmatics, probably by reducing the RhoA-mediated signaling.

In mice previously sensitized to Ovalbumin, Simvastatin treatment, either orally or intraperitoneally, reduced the total inflammatory cell infiltrate and eosinophilia in bronchoalveolar lavage fluid in response to inhaled ovalbumin challenge. Simvastatin therapy i.p. was also associated with a reduction in IL-4 and IL-5 levels in bronchoalveolar lavage fluid and, higher doses, a histological reduction in inflammatory infiltrates in the lungs. Ovalbumin-induced IL-4, IL-5, IL-6, and IFN-gamma secretion was reduced in thoracic lymph node cultures from Simvastatin-treated mice. Simvastatin treatment did not alter serum total IgE or OVA-specific IgG1 and IgG2a levels. These data demonstrate the therapeutic potential of statin-sensitive pathways allergic airways disease**.**

Clinical study of statins on lung function [55]

The effect of statin use on decline in lung function in the elderly, and whether smoking modified this effect was investigated.Study population included 2,136 measurements on 803 elderly men from the Normative Aging Study whose lung function (FVC and FEV_1) was measured two to four times between 1995 and 2005. Subjects indicated statin use and smoking history at each visit. They used mixed linear models to estimate the effects of each covariate, adjusting for subject and possible confounders. For those not using statins, the estimated

decline in FEV_1 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 FEV_1 (95% CI, –16.9 to –5.0 ml/yr). These results indicate that statin use attenuates decline in lung function in the elderly, with the size of the beneficial effect modified by smoking status bronchoalveolar lavage cells and lung tissues. In clinical studies, lung transplant recipients with statin therapy had a better survival rate than those without it.[56] This result was probably reflected by down regulation of myofibroblast function with statin.[57]

These clinical studies support the beneficial effects of statins probably by the anti inflammatory and immunomodulatory effects, which encouraged me take up this study of Atorvastatin in chronic asthma, done at Government General hospital, Chennai on patients attending Chest Medicine out patient department.

OBJECTIVES

OBJECTIVES

- To evaluate the efficacy of Atorvastatin as an adjuvant in the treatment of chronic moderate-severe,stable asthma.

- To asses the tolerability of Atorvastatin in asthma patients.

METHODOLOGY

METHODOLOGY

STUDY DESIGN:

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

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

STUDY PERIOD: Sep 2007 to Mar 2008

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 bronchodialators,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,azoleantifungals, digoxin,protease inhibitors etc.
- Pregnant and lactating women

STUDY PROCEDURE:

ETHICAL CONSIDERATION:

The study was commenced after obtaining approval from the Institutional Ethical Committee. Patients with chronic asthma attending the Chest Medicine OPD, Government General Hospital, Chennai, who were already on standard treatment for asthma, were explained about the purpose of the study, study procedure and possible side effects in local vernacular language. Written informed consent was obtained from those who were willing to participate in the study in the prescribed format in regional language. Left thumb impression was obtained from those patients who are illiterates. This was done in the presence of impartial witness.

SCREENING:

Patients who were willing to participate were registered for the study. Detailed medical history and demographic details were obtained from all patients who gave informed consent for the study.

Baseline investigations:

TC, ESR, Hb

Absolute eosinophil count

Random Blood sugar

Serum urea, creatinine

SGPT, SGOT

Lipid profile (cholesterol,triglycerides)

ECG, Chest X Ray

Spirometry

Asthma control score

RECRUITMENT:

Among 206 patients screened, 90 patients who fulfilled the inclusion criteria were recruited for the study. They were randomly allocated into 3 groups (A, B, & C) each containing 30 patients by simple randomization method.

Treatment schedule:

Group A (standard treatment) (n = 30)

Tab.Salbutamol 4 mg twice daily

Tab.Deriphylline 100 mg thrice daily

Group B(n=30)

Standard treatment +Atorvastatin 10 mg OD

Group C(n=30)

Standard treatment + Atorvastatin 20 mg OD

Visits to receive drugs:

Drugs were issued for 2 weeks only. At the end of 2 weeks, they were asked to return the empty packs (to check the compliance) and receive the drugs for the subsequent 2 weeks. The same procedure was followed for 8 weeks. Any adverse effect reported by the patient or observed by the physician

during the study was recorded. If the patient experiences adverse effect, he/she was advised to report immediately to the investigator without fail.

Follow up visits:

Follow up visit 1 (at the end of 4 weeks)

Follow up visit 2 (at the end of 8 weeks)

ASSESSMENT OF EFFICACY:

1.Spirometry (FEV_1, PEF<peak expiratory flow>) measurement at baseline, 4 and 8 weeks

2. Lab parameters (absolute eosinophil count, erythrocyte sedimentation rate) at baseline ,4 weeks and 8 weeks.

3. Asthma control score (ACS)

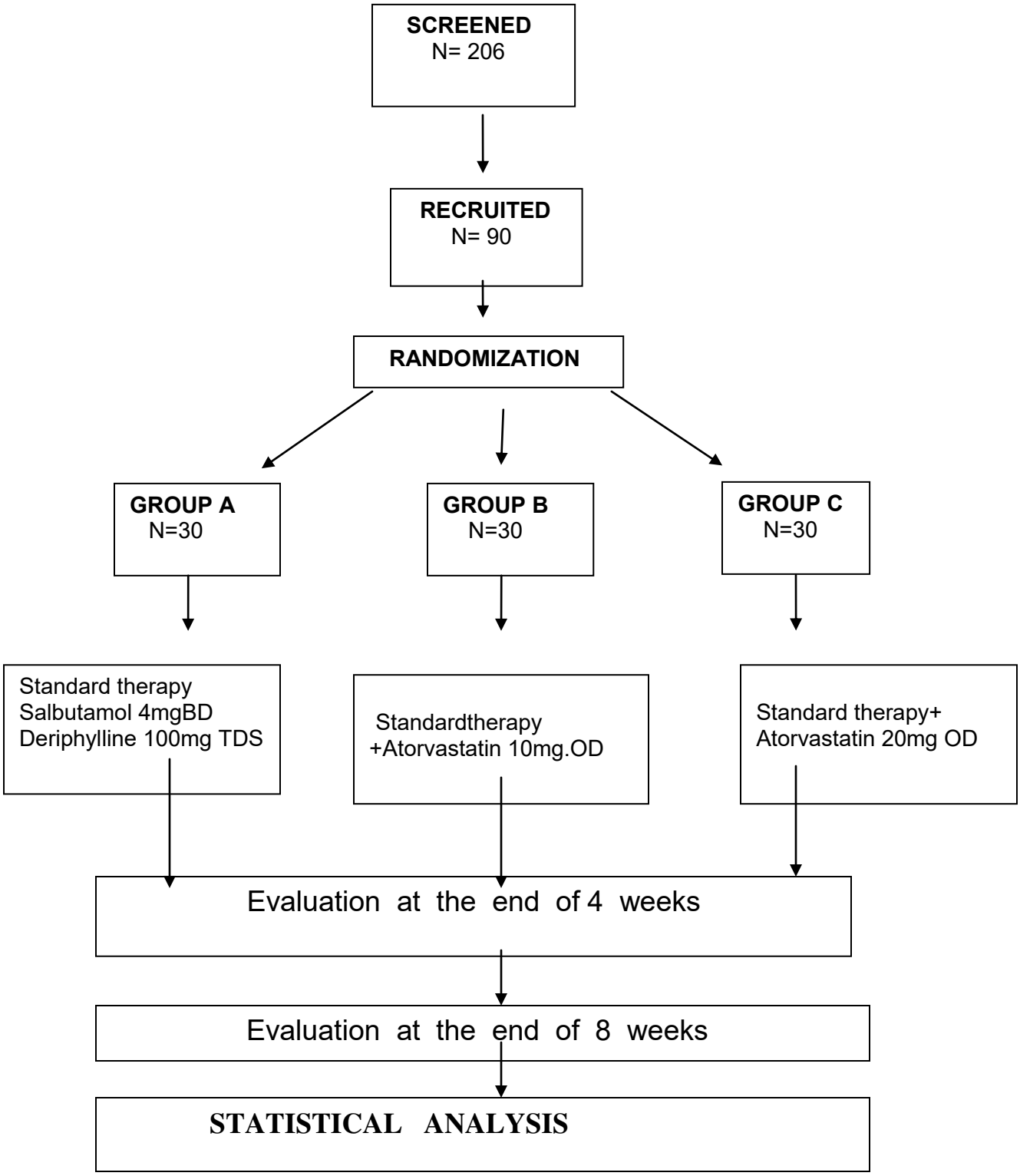
ACS is a combined subjective index to measure the disease activity of asthma which consists of the following informations(annexure)

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

STATISTICAL ANALYSIS

Statistical analysis was done with one way ANOVA and multiple comparisons with Bonferroni T test.

STUDY PROCEDURE FLOW CHART



RESULTS

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 exsmokers,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 deriphylline200 mg thrice daily . Group B, C received in addition atorvastatin 10, 20 mg 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; AGE DISTRIBUTION

Group	No. of patients	Mean Age + SD	One way ANOVA F-test
Group A Group B Group C	30 30 30	38.96±10.57 40.3± 10.75 37± 10.6	F=0.73 P=0.48 Not significant

Figure 1: AGE DISTRIBUTION

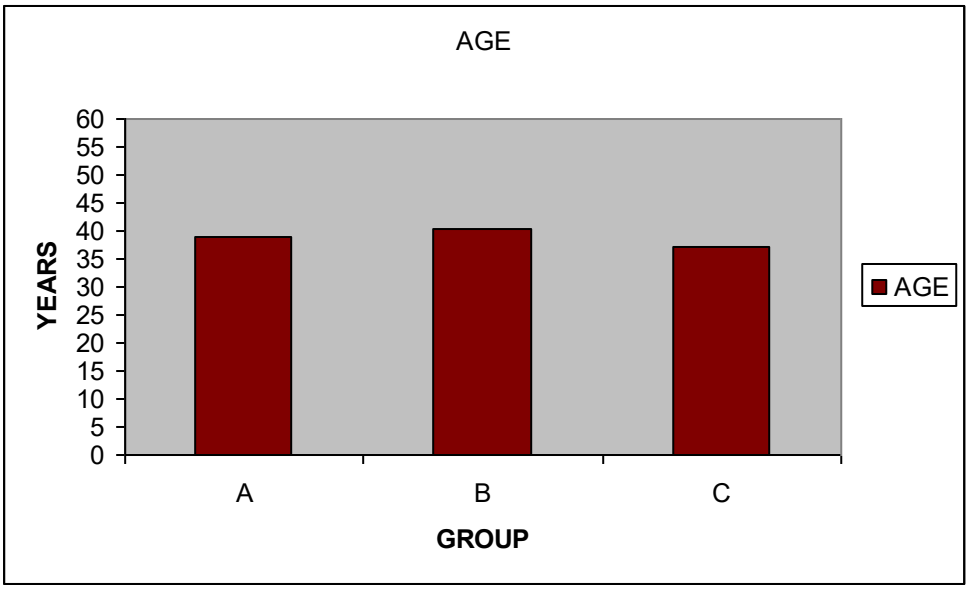


Table: 1 shows

The mean age distribution was even in all the study groups

There was no statistically significant difference among study groups.

Figure: 1 is the diagrammatic representation of the mean age distribution in study groups.

Table 2: **BODY MASS INDEX**

Group	No. of patients	BMI Mean+SD	One way ANOVA F-test
Group A **Group B** **Group C**	30 30 30	23.4+1.91 23.66+1.75 23.61+1.43	F=0.98 P=0.83 Not significant

Figure 2: **BODY MASS INDEX**

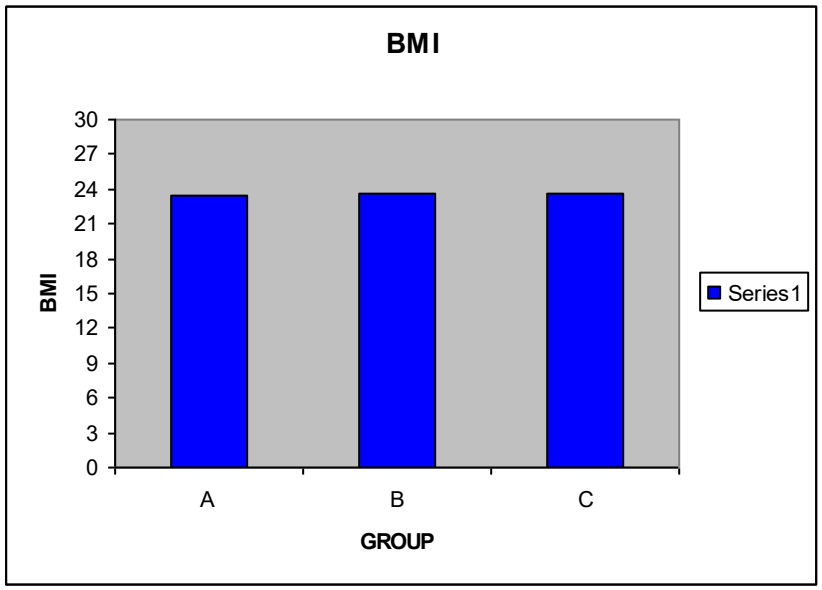


Table: 2 shows

The mean body mass index of patients in each study group. There was no statistically difference among groups regarding BMI (p=0.83).

Figure: 2 is the diagrammatic representation of the mean BMI of patients in each group.

Table: 3 SEX DISTRIBUTION

Groups	Sex				Chi square test
	Male		Female		
	n	%	n	%	
Group A	7	23.33%	23	76.66%	$\chi 2=0.008$ P=1.00 Not significant
Group B	7	23.33%	23	76.66%	
Group C	8	26.66%	22	73.33%	
Total	22	24.44%	68	75.56%	

Figure 3 **SEX DISTRIBUTION**

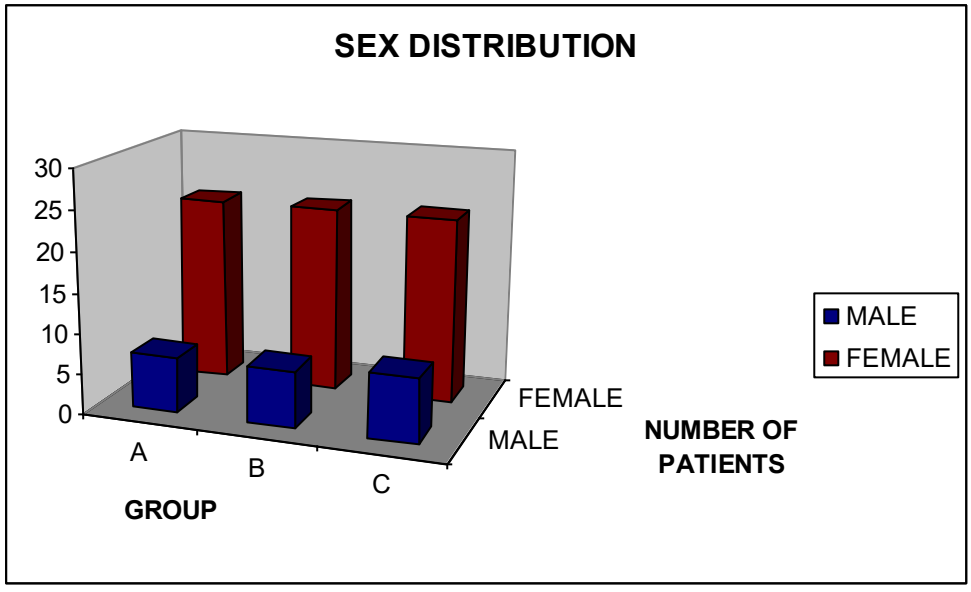


Table: 3 shows

The sex distribution in the study groups.

There was no statistically significant difference among groups in sex distribution.

Figure:3 is the diagrammatic representation of sex distribution among the three groups

Table 4 **Mean Duration of illness**

GROUPS	Mean duration of illness(in years)
GROUP A	16.06
GROUP B	15.33
GROUP C	15.26

Figure 4 **Duration of illness among groups**

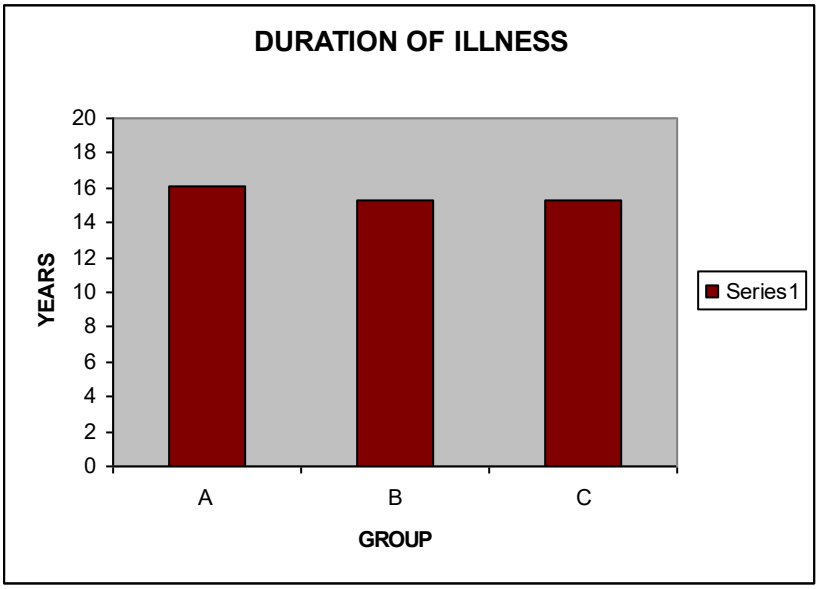


Table: 4 shows

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

Table 5: Comparison of ACS score

GROUP	**BASELINE** Mean ± SD	**AFTER 4WEEKS** Mean ± SD	**AFTER 8WEEKS** 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
ONEWAY ANOVA F-TEST	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 5: comparison of ACS score

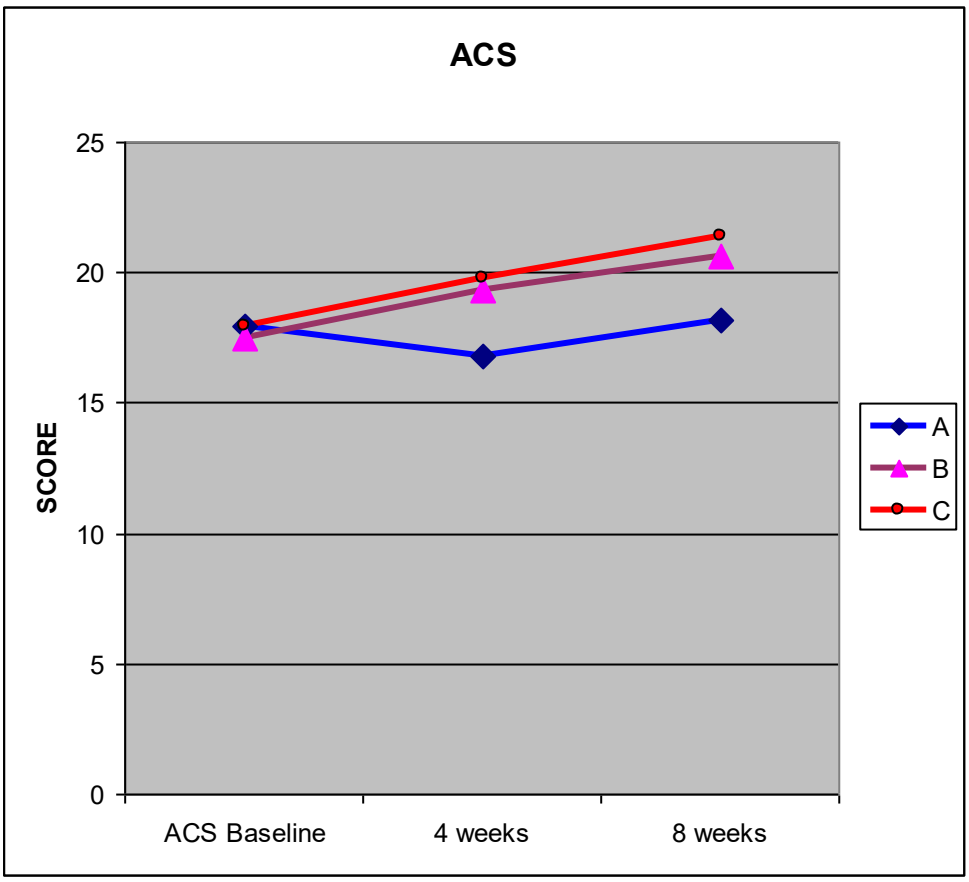


Table 5

- 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

Figure 5 is the diagrammatic representation of ACS score in all the study groups at baseline, 4 and 8 weeks.

Table 6 **FORCED EXPIRATORY VOLUME(1SECOND)**

GROUP	FEV1 BASELINE Mean +S.D	FEV1 4 WEEKS Mean+S.D	FEV1 8 WEEKS Mean+S.D
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

Figure 6 **FORCED EXPIRATORY VOLUME(1SECOND)**

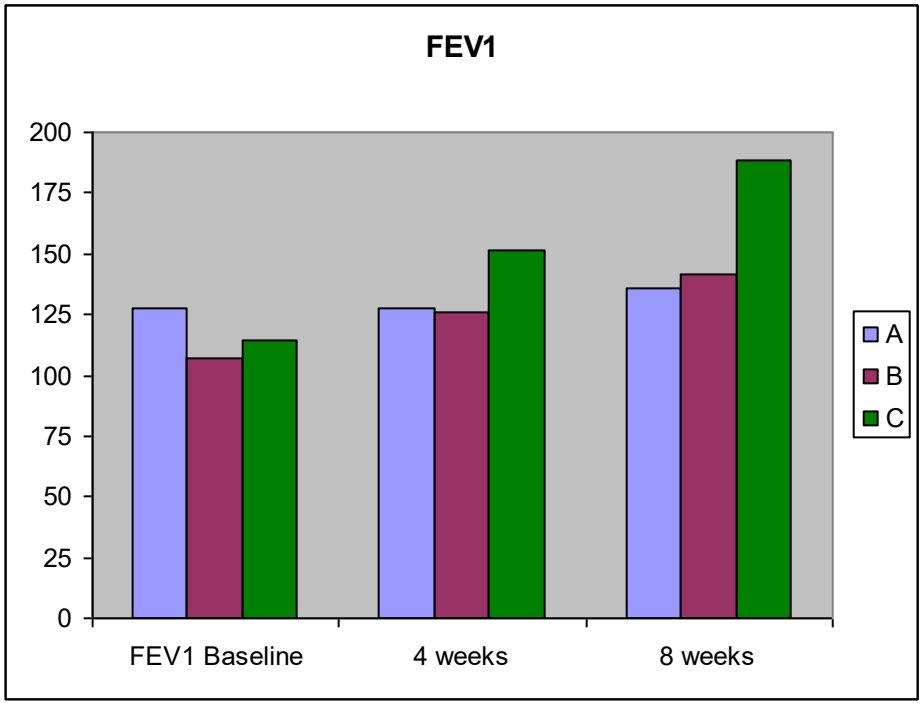


Table 6

- 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)

- 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 6 is the diagrammatic representation of FEV1 at baseline, 4 weeks and 8 weeks in all the groups

Table 7: PEAK EXPIRATORY FLOW

GROUP	PEFR BASELINE Mean+S.D	PEFR 4 WEEKS Mean+S.D	PEFR 8 WEEKS Mean+S.D
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 VsC=0.51

Figure 7: PEAK EXPIRATORY FLOW

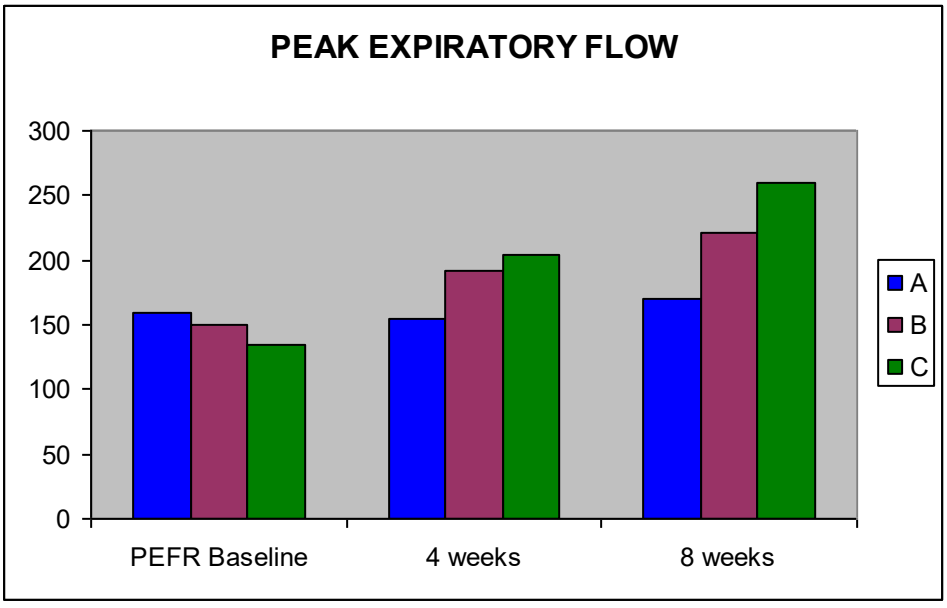


Table 7 shows

- PEF at baseline is not significant in all the groups

- PEF at 2 months 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 7 is the diagrammatic representation of PEF at baseline4 and 8 weeks in all the groups

Table 8 ERYTHROCYTE SEDIMENTATION RATE

GROUP	ESR BASELINE	4 WEEKS	8 WEEKS
GROUPA	14.46±2.23	12.5±1.38	11.36±1.21
GROUP B	16.36±2.28	13.5±1.85	11.3±1.29
GROUP C	17.86±2.44	14.13±2.25	11.46±1.07
ONEWAY ANOVA F-TEST	F=0.15 P=0.86 Not Significant	F=5.97 **P=0.003** **Significant**	F=16.13. **P=0.001** Significant
BONFERRONI T-TEST			***AVsB=0.006*** ***AVsC=0.001*** ***BVsC=0.043***

Table 9: ABSOLUTE EOSINOPHIL COUNT

GROUP	AEC BASELINE Mean+S.D	AEC 4 WEEKS Mean+S.D	AEC 8 WEEKS Mean+S.D
GROUP A	465.5+61.22	442.16+50.3	420+46
GROUP B	509.3+145.2	440+998.96	392+33
GROUP C	531+87.62	472.33+78.98	416.6+82
ONE WAY ANOVA F TEST	F=3 p=0.06 Not significant	F=1.58 p=0.21 Not significant	F=1.39 p=0.25 Not Significant
BONFERRONI T TEST			A Vs B=0.32 **A Vs C=0.048** **Significant** B VsC=1.0

Table 10 TOTAL LEUCOCYTE COUNT(TC)

GROUP	TC BASELINE Mean+S.D	TC 4 WEEKS Mean+S.D	TC, 8 WEEKS Mean+S.D
GROUP A	9240+256	9240+256	9220+274
GROUP B	9310+263	9310+263	9273+267
GROUP C	9236+256	9236+256	9220+274
ONE WAY ANOVA F TEST	F=0.77 p=0.46 Not significant	F=0.77p=0.46 Not significant	F=0.38 p=0.68 Not Significant

Table 8

- Shows no statistical significance for ESR at baseline in all the groups

- Shows statistically significant difference for ESR between groupA and B , and between group A and C at 4 and 8 weeks

- There is also a statistically significant difference between group B and C which proves that higher dose is more beneficial for asthmatics

Table 9

- Shows no statistical significane at baseline, 4 and 8 weeks for absolute eosinophil count in all groups

- Show statistical significance between group A and C which shows that higher dose of atorvastatin is beneficial in reducing the ESR level in asthmatics

Table 10

Mean total leucocyte count is statistically insignificant at baseline, 4 and 8 weeks in all the groups

Table 11 CREATINE PHOSPHO KINASE(mg/dl)

GROUP	CPK BASELINE Mean+S.D	CPK 4 WEEKS Mean+S.D	CPK 8 WEEKS Mean+S.D
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=2.87p=0.063 Not significant	F=0.79 p=0.45 Not Significant

Table 12 UREA(mg/dl)

GROUP	CPK BASELINE Mean+S.D	CPK 4 WEEKS Mean+S.D	CPK 8 WEEKS Mean+S.D
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=2.87p=0.063 Not significant	F=0.79 p=0.45 Not Significant

Table 13: SERUM CREATININE(mg/dl)

GROUP	CREATININE BASELINE Mean+S.D	CREATININE 4 WEEKS Mean+S.D	CREATININE 8 WEEKS Mean+S.D
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=1.19p=0.309 Not significant	F=0.46 p=0.631 Not Significant

Table 11 shows

Mean creatine phosphokinase is statistically insignificant at baseline, 4 and 8 weeks in all the groups.

Table 12 shows

Mean serum urea concentration shows no statistical significance at baseline, 4 and 8 weeks in all the groups.

Table 13 shows

There is no statistical difference in mean serum creatinine between the three groups at baseline 4 and 8 weeks.

Table 14: SERUM GLUTAMIC PYRUVATE TRANSAMINASE (SGPT)

GROUP	SGPT BASELINE Mean+S.D	SGPT 4 WEEKS Mean+S.D	SGPT 8 WEEKS Mean+S.D
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=0.09p=0.0913 Not significant	F=0.48 p=0.618 Not Significant

Table 15: SERUM GLUTAMIC OXALOACETATE TRANSAMINASE (SGOT)

GROUP	SGOT BASELINE Mean+S.D	SGOT 4 WEEKS Mean+S.D	SGOT 8 WEEKS Mean+S.D
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 14 shows

There is no statistical difference of mean SGPT in all the groups at baseline, 4 and 8 weeks.

Table 15 shows

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

Table 16: SERUM CHOLESTEROL

GROUP	CHOLESTEROL BASELINE Mean+S.D	CHOLESTEROL 4 WEEKS Mean+S.D	CHOLESTEROL 8 WEEKS Mean+S.D
GROUP A	189.7+24.8	185+25.5	186.2+19.8
GROUP B	185.9+34.6	163+33.1	156.1+27.9
GROUP C	186.9+31.4	168.1+30.7	169.2+29.05
ONE WAY ANOVA F TEST	F=0.13 p=0.88 Not significant	F=4.13p=0.019 Significant	F=10.16p=0.001 Significant

Table 17: SERUM TRIGLYCERIDES

GROUP	TGL,BASELINE Mean+S.D	TGL, 4 WEEKS Mean+S.D	TGL, 8 WEEKS Mean+S.D
GROUP A	104.45+18.2	112.6+33.4	113.2+31..2
GROUP B	106.4+21.7	124+32.8	110+26.8
GROUP C	103+21.9	119+31.9	110.8+24.16
ONE WAY ANOVA F TEST	F=0.17 p=0.84 Not significant	F=0.91p=0.406 Not significant	F=0.07 p=0.92 Not Significant

Table 16 shows

There is statistical significance in mean serum cholesterol at, 4 and 8 weeks in all the groups(**p=0.019** at 4 weeks,**p=0.001** at 8 weeks)

Table 17 shows

There is no statistical significance in mean serum triglycerides at baseline, 4 and 8 weeks in all the groups

Table 18: ADVERSE EVENTS

ADVERSE EVENTS	GROUPA	GROUPB	GROUPC
MYALGIA	1	1	2
NAUSEA	1	1	1
DYSPEPSIA	2	2	1

Figure 8: ADVERSE EVENTS

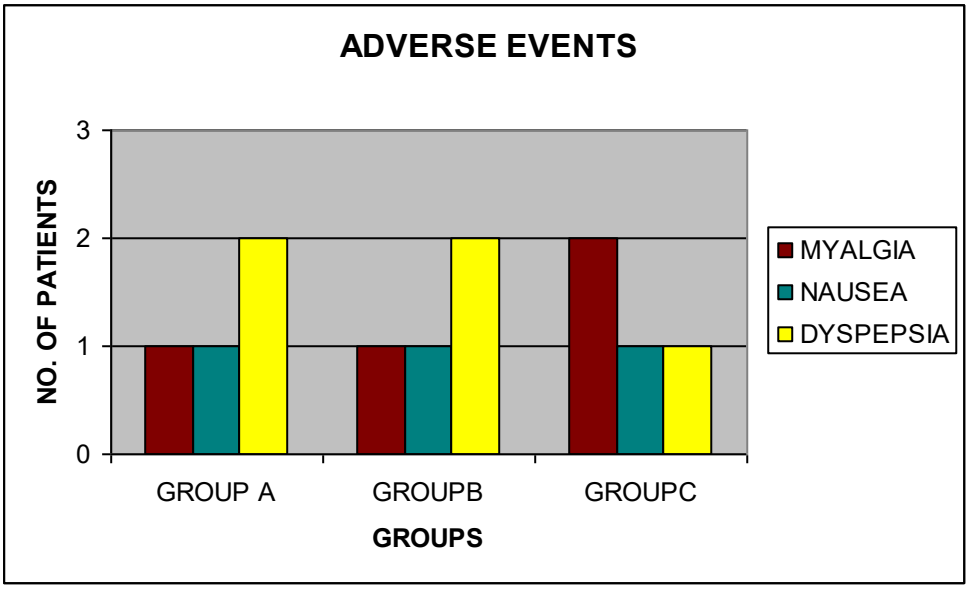


Table 18shows

Adverse events equally distributed among the three groups during the study period.

Figure 8 is the diagrammatic representation of adverse events in the three groups during the study period

DISCUSSION

DISCUSSION

Asthma is a chronic inflammatory disease of the lung characterized by episodic airway obstruction and increased bronchial responsiveness [58]. 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.[59] It is now widely accepted that in asthmatics, recruitment of inflammatory cells , in particular eosinophils and T cells , also occurs in the distal lung[60,61]and the lung parenchyma.[62]At this distant site there are an abundance of T Helper -2 cytokines and chemokines [61,63]and pro inflammatory mediators including cyclo- oxygenase metabolites.[64] 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.[65]

In the Normative Aging Study done at Boston, Massachusetts conducted with 803 elderly men whose lung function (FVC and FEV_1) was measured two to four times between 1995 and 2005 , it was observed that, for

those not using statins, the estimated decline in FEV_1 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 FEV_1 (95% CI, –16.9 to –5.0 ml/yr),which indicated that statin use attenuates decline in lung function in the elderly [55].

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 [66].

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). FEV_1 values increased significantly (p=0.001) at 8 weeks in group C .FEV_1 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 [55] .

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.[67] 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,[67] 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

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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APPENDICES

ABBREVIATIONS

ACT	Asthma control Test Score
Ach	Acetyl choline
AEC	Absolute eosinophil count
ANOVA	Analysis of variance
BMI	Body mass index
BSM	Bronchial smooth muscle
CD	Cluster of differentiation
COPD	Chronic obstructive pulmonary disease
Co Q	Coenzyme Q
CPK	Creatine phosphokinase
CSAIDS	Cytokine suppressant anti-inflammatory drugs
CYP	Cytochrome P 450
ESR	Erythrocyte sedimentation rate
FEV1	Forced expiratory volume in first second
FVC	Forced vital capacity
GTP	Guanosine triphosphate
HDL-C	High density lipoprotein cholesterol
HETE	Hydroxy eicosatetraenoic acid

HMGCoA	3-Hydroxy 3-methyl coenzyme A
IFN	Interferon
Ig E	Immunoglobulin
I.P	Intraperitoneal
LFA	Long chain fatty acid
LT	Leukotriene
LDL-C	Low density lipoprotein cholesterol
LO	Lipoxygenase
MAP	Mitogen activated protein
MMP	Matrix metalloproteinase
NK Cells	Natural killer cells
OPD	Out patient department
PEFR	Peak expiratory flow rate
PG	Prostaglandin
SGOT	Serum glumatic oxaloacetate transaminase
SGPT	Serum glutamic pyruvate transaminase
S D	Standard deviation
TNF	Tumour necrosis factor
Th	T- helper
TLC	Total leucocyte count

Enter Name

Enter Address

Enter City/State/Zip

Today's Date: _____

Patient's Name: _____

FOR PATIENTS:

Take the Asthma Control Test™ (ACT) for people 12 yrs and older.

Know your score. Share your results with your doctor.

Step 1 Write the number of each answer in the score box provided.

Step 2 Add the score boxes for your total.

Step 3 Take the test to the doctor to talk about your score.

										SCORE
1. In the past **4 weeks**, how much of the time did your **asthma** keep you from getting as much done at work, school or at home?	All of the time	1	Most of the time	2	Some of the time	3	A little of the time	4	None of the time	5	
2. During the past **4 weeks**, how often have you had shortness of breath?	More than once a day	1	Once a day	2	3 to 6 times a week	3	Once or twice a week	4	Not at all	5	
3. During the past **4 weeks**, how often did your **asthma** symptoms (wheezing, coughing, shortness of breath, chest tightness or pain) wake you up at night or earlier than usual in the morning?	4 or more nights a week	1	2 or 3 nights a week	2	Once a week	3	Once or twice	4	Not at all	5	
4. During the past **4 weeks**, how often have you used your rescue inhaler or nebulizer medication (such as albuterol)?	3 or more times per day	1	1 or 2 times per day	2	2 or 3 times per week	3	Once a week or less	4	Not at all	5	
5. How would you rate your **asthma** control during the **past 4 weeks**?	Not controlled at all	1	Poorly controlled	2	Somewhat controlled	3	Well controlled	4	Completely controlled	5	
											TOTAL

If your score is 19 or less, your asthma may not be controlled as well as it could be. Talk to your doctor.

FOR PHYSICIANS:

The ACT is:

- A simple, 5-question tool that is self-administered by the patient
- Clinically validated by specialist assessment and spirometry[1]
- Recognized by the National Institutes of Health

Reference: 1. Nathan RA et al. *J Allergy Clin Immunol.* 2004;113:59-65.

Patient consent form

Study Title: **EFFICACY AND TOLERABILITY OF ATORVASTATIN AS AN ADD-ON THERAPY IN THE TREATMENT OF CHRONIC STABLE (MODERATE-SEVERE) ASTHMA**

Study Centre: Chest Medicine OPD, GGH, Chennai.

Patient's Name: _____

Patient's Date of Birth: _____

Identification Number: _____

Patients may check (✓) these boxes.

I confirm that I have read and understood the information sheet for the above study. I have the opportunity to ask question and all my questions and doubts have been answered to my complete satisfaction.	
I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving any reason and without my legal rights being affected.	
I understand that the ethics committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the study. I agree to this access. However, I understand that my identi1' will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study.	
I agree to take part in the above study and to comply with the instructions given during the study and to faithfully co-operate with the study team, and to immediately inform the study staff if I suffer from any deterioration in my health or well being or any unexpected or unusual symptoms.	
I hereby consent to participate in this study of efficacy and tolerability of atorvastatin as an add-on therapy in the treatment of chronic stable (Moderate-severe) Asthma and I understand that I will be treated with Atorvastin orally once daily.	
I hereby give permission to undergo complete Physical examination, and Diagnostic tests including hematological, biochemical, radiological and electrocardiogram	

Signature / Thumb Impression _____ Place Date
Of the Patient / Attender.

Patient's Name & Address: _____

Signature of the Investigator _____ Place _____ Date

Study Investigator's Name: _____

Institution _____

Signature of the Witness _____ Place _____ Date

Name & Address of the witness: _____

*Mandatory for uneducated patients (Where thumb impression has been provided above).