A RANDOMISED, OPEN LABEL, COMPARATIVE, PROSPECTIVE, PARALLEL GROUP STUDY OF ATORVASTATIN AS AN ADD ON THERAPY TO STANDARD THERAPY IN REDUCING DISEASE ACTIVITY OF RHEUMATOID ARTHRITIS

Dissertation submitted to

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY

in partial fulfillment for the award of the degree of

DOCTOR OF MEDICINE

IN

PHARMACOLOGY

INSTITUTE OF PHARMACOLOGY
MADRAS MEDICAL COLLEGE
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CERTIFICATE

This is to certify that the dissertation entitled, **"A RANDOMISED, OPEN LABEL, COMPARATIVE, PROSPECTIVE, PARALLEL GROUP STUDY OF ATORVASTATIN AS AN ADD ON THERAPY TO STANDARD THERAPY IN REDUCING DISEASE ACTIVITY OF RHEUMATOID ARTHRITIS",** submitted by **Dr.B.Meenakshi,** 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 her in the Institute of Pharmacology, Madras Medical College, during the academic year 2005 – 2008.

DEAN
MADRAS MEDICAL COLLEGE &
GOVT. GENERAL HOSPITAL,
CHENNAI – 600 003.

DIRECTOR AND PROFESSOR,
INSTITUTE OF PHARMACOLOGY,
MADRAS MEDICAL COLLEGE,
CHENNAI – 600 003.

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CONTENTS

INTRODUCTION

INTRODUCTION

Rheumatoid arthritis (RA) is the most common inflammatory arthritis affecting 0.5 to 1 % of the general population worldwide.[1] Women are affected approximately three times more than men. The onset is most frequent during the fourth decade of life with 80% of all patients developing the disease between the ages of 35 and 50. [2]

Rheumatoid arthritis is not a benign disease. A 25-year-old prospective study showed that median life expectancy is shortened by 7 years in males and 3 years in females. [3]

Rheumatoid arthritis typically presents as symmetric arthritis principally affecting the small joints of hands and feet, ankles, knees, wrists, elbows and shoulders. It is proposed that the disease is initiated in a genetically predisposed individual by activation of helper T cells responding to some arthritogenic agents possibly microbials. In turn, the activated CD4+ cells produce cytokines that will activate macrophages and other cells in the joint space, releasing degradative enzymes and other factors that perpetuate inflammation and activate B cells, resulting in the production of antibodies, some of which are directed against self constituents. The rheumatoid synovium is rich in both lymphocyte and macrophage derived cytokines. The activity of these cytokines accounts for many features of RA. They are not only proinflammatory, some, such as interleukin 1 (IL-1) and transforming growth factor alpha (TGF α) also cause synovial cell and fibroblast proliferation. They also stimulate synovial cell and chondrocyte secretion of proteolytic and matrix degrading enzymes. [4]

Helper T cells have been divided into cytokine specific subsets. T Helper 1(Th1) cells produce interferon gamma (IF γ), IL-2 and IL-17 but not IL-4, IL-5 or IL-10. In contrast, T helper 2 (Th2) cells produce the opposite profile IL4+, IL10+. Th1 cells primarily mediate delayed type hypersensitivity in vivo, whereas Th2 cells are more predominant regulator of isotope switching and antibody production. Some cytokines produced by Th2 cells are immunosuppressive, because IL-4 and IL-10 down regulate Th1 cell differentiation.[1] Within the rheumatoid synovium the CD4+ T cells differentiate predominantly into Th1 like effector cells producing proinflammatory cytokine interferon gamma and appear to be deficient in differentiation into Th2 like effector cells producing the anti-inflammatory cytokine IL-4. [2]

Although RA is properly considered as a disease of joints it can cause a variety of extra articular manifestation.[1] It is now becoming clearer that patients with RA are prone to develop macro vascular injury leading to coronary artery disease .[5]

There is an association between the level of acute phase reactant, C reactive protein (CRP) and disease activity score in RA.[6] Increased CRP in RA in response to acute stress reflects an increased risk of myocardial infarction in these patients.

Statins have been suggested to reduce inflammatory cytokine production, like tumor necrosis factor alpha and IL-1 β chemo tactic cytokine like IL-delta and IL-6. [7-9] As most of these above said events are central to RA, statins are expected to be useful in RA.

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. Oral atorvastatin was recently shown to prevent or reverse chronic or relapsing paralysis due to demyelinization in a murine model. This was associated with a shift from Th1 type immune response to Th2 type responses in vivo.[10, 11] Furthermore two of three recent studies have demonstrated clinically apparent anti-inflammatory effects of statins in recent models and in patients with RA.[12-15.]

Atorvastatin for 8 days (20mg/day) in patients with rheumatoid arthritis showed reduction in C reactive protein levels and clinical improvement. Prior to the administration of statins all these patients had received aggressive conventional therapy with no satisfactory response .[16]

This study was taken up to evaluate the efficacy of atorvastatin in different dosages (5mg, 10mg and 20 mg) in RA in our community.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Rheumatoid arthritis (RA) is a chronic multisystem disease of unkonwn cause. Although there are a variety of systemic manifestations, the characteristic feature of RA is persistent inflammatory synovitis, usually involving peripheral joints in a symmetric distribution.[2]

History of RA:

The name is derived from the Greek. Rheumatos means “flowing” and this initially gave rise to the term “rheumatic fever”, an illness that can follow throat infections and which includes joint pain. The suffix-oid means “resembling” ie. resembling rheumatic fever. Arthr means “joint” and the suffix “itis”, a “condition involving inflammation”. Rheumatoid arthritis appears to have been described in paintings more than a century before the first detailed medical description of the condition in 1800 by Landre –Beauvais. [17]

Epidemiology and genetics:

The prevalence of RA is approximately 0.8 % of the population.[2]The ratio of female to male patients is 2:1 to 4:1. The basis of the gender differences is not known, but presumably is related to effects of the hormonal milieu on immune function. Pregnancy is often associated with remission of the disease in the last trimester. More than three quarters of the patients with RA improve, starting in the first or second trimester; but 90% experience a flare of disease associated with a rise in RF titres in the weeks or months after delivery. The mechanism of protection is not defined but might be due to the expression of suppressive cytokines such as interleukin 10(IL 10) during pregnancy or alterations

in cell-mediated immunity.[1] The class II major histocompatability complex allele HLA-DR 4 and related alleles are known to be major genetic
risk factors for RA.[2]

Etiology:[2]

The cause of RA remains unknown. It has been suggested that RA might be a manifestation of the response to an infectious agent in a genetically susceptible host. A number of possible causative agents have been suggested including mycoplasma, Ebstein Barr virus, cytomegalovirus, parvovirus and rubella virus. One possibility is that there is a persistent infection of articular structures or retention of microbial products in the synovial tissues that generate a chronic inflammatory response. Alternatively, the microorganism might induce an immune response to components of joint by altering its integrity and revealing antigenic peptides.

Another possibility is that the infecting microorganism might prime the host to cross-reactive determinants expressed within the joint as a result of 'molecular mimicry".

Finally, products of infecting microorganisms such as super antigens might induce the disease.

Synovial Pathology and Biology;

The primary site of immune activation in RA is the synovium. Infiltration of the synovium with mononuclear cells, especially T cells and macrophages, and synovial intimal lining hyperplasia are hallmarks of the disease. The increase in cell number in RA can be quite substantial. In the normal joint, the lining is only

one to two cell layers deep, whereas in RA it is often four to 10 cells deep (and sometimes more than 20).[1]The relative abundance of helper T cells 1 (Th1 cells) and cytokines suggests that the synovium participates in an unregulated Th1 like delayed type hypersensitivity reaction. T helper cells 2 (Th2) cytokine and cellular responses that normally suppress Th1 activation are nearly absent, thereby raising the possibility that lack of T cell activation along the Th2 pathway in RA contributes to disease perpetuation.[1]

Clinical features

RA usually has an insidious, slow onset over weeks to months. The initial symptoms may be systemic or articular. The joints most commonly involved first in RA are metacarpophalangeal joints (MCP), proximal interphalangeal (PIP), metatarsophalangeal joints and wrists.[18] Morning stiffness of greater than 1-hr duration is an almost invariable feature of inflammatory arthritis and may serve to distinguish it from various noninflammatory disorders.[2] The majority of patients will experience constitutional symptoms such as weakness, easy fatigability, and anorexia and weight loss.[2]

Extra articular manifestations:

Local- Rheumatoid nodules are the most common, and are found in areas susceptible to trauma, such as elbows. They consist of palisade of macrophages surrounding fibrous tissue.

Systemic-In more severe cases there may be vasculitis, fibrosis lungs and serositis as characterized by pericarditis and pleurisy.

American College of Rheumatology (ACR) Diagnostic criteria:[20]

4 of the following must be present with 1 through 4 present a minimum of 6 weeks

- Morning stiffness ≥ 1 hr
- Arthritis of 3 or more of the following joints: right or left PIP, MCP, wrist, elbow, knee, ankle and MTP joints
- At least one area swollen in a wrist or MCP or PIP joints
- Symmetric involvement of joints
- Rheumatoid nodules over bony prominences or extensor surfaces or in juxtaarticular regions
- Positive serum rheumatoid factor
- Radiographic changes including erosions or bony decalcification localized in or adjacent to the involved joints.

Laboratory findings in RA:

Haematological abnormalities:

Erythrocytes: Anaemia is a common finding in patients with active RA. Typically the anaemia is normocytic and either normochromic or hypochromic.[21] Because Transferrin behaves as an acute phase protein it is frequently elevated in patients with RA and does not necessarily reflex iron stores.[22] Although there may be other factors contributing to the anaemia seen in patients with RA, the predominant cause is the so-called anaemia of chronic disease.[23] This anaemia is probably due to underproduction of red blood cells.[24]

Leukocytes; In contrast to its effects on erythroid precursors interleukin 1b (IL-1b) does not inhibit colony forming units-granulocyte- macrophage (GM-CFU) .In

fact, IL-1b increases the production of both granulocyte-macrophage colony stimulating factor (GM-CSF) and granulocyte colony stimulating factor (G-CSF).[23] TNF-α has a similar effect and may increase CSF-GM.[25] Eosinophilia may occur in patients with severe disease or those with high titre rheumatoid factor.[26]

Platelets; Platelet counts are frequently elevated in patients with RA and this generally correlates with anaemia, leukocytosis and titre of RF.[27]

ESR: The most frequently used laboratory measure of inflammation or "disease activity" in RA is erythrocyte sedimentation rate. ESR does correlate with activity of disease in RA. Worsening disease is usually associated with an increase in ESR, and remission with normalization of this test.[21]

C-reactive protein (CRP): Acute phase proteins are frequently elevated in patients with RA. These proteins are produced predominantly by the liver in response to certain cytokines, many of which are produced in excess in patients with RA.[21]Serum amyloid A and CRP increase very rapidly over hours, after the acute phase response is initiated. They peak in 1 to 3 days and levels return rapidly back to baseline after the acute event has resolved.[28]

Rheumatoid factor (RF): The association between elevated serum RF and RA was first noted in the late 1930s by Waaler and subsequently by Rose and colleagues. Originally called agglutination activating factor, the term rheumatoid factor was coined in 1949 by Pike and colleagues.[29]

RF consists of a heterogenous population of auto antibodies reactive with a multiplicity of determinants localized to the Fc portion of IgG. RF can also be seen in normal individuals and those with a variety of chronic inflammatory or

infectious diseases. The presence of RF in a multitude of conditions other than RA, limits the disease specificity of the test. Further more the fact that serum RF is not found in all individuals with RA, limits the sensitivity of the test in the diagnosis of RA. Although RF assay may not be particularly useful in diagnosing RA or other rheumatic diseases in patients in general population, it does have usefulness in a highly selected group of patients, namely those in a rheumatology out patient clinic.[29]

A number of conditions besides RA are associated with the presence of RF. These include systemic lupus erythematosus, Sjogren's syndrome, chronic liver disease, sarcoidosis, interstitial pulmonary fibrosis, infectious mononucleosis, hepatitis B, TB, leprosy, syphilis, subacute bacterial endocarditis, visceral leishmaniasis, schistosomiasis and malaria. A test for the presence RF can be employed to confirm a diagnosis in individuals with a suggestive clinical presentation and if present in high titre, to designate the patients at risk for severe systemic disease.[2]

Complications:

In a 25-year prospective follow-up of 209 patients with rheumatoid arthritis, median life expectancy was shortened by 7 years in males and by 3 years in females when compared with the general population. The surplus mortality was associated in decreasing order with the disease itself, associated respiratory, urogenital and general infections, and with upper gastro intestinal tract disease mainly bleeding.[3] Rheumatoid arthritis is associated with

accelerated vascular risk with attendant early mortality (pooled standardized mortality rate 1.7) and excess morbidity.[30]

Management of RA:

Because the exact cause and pathogenesis of RA remains uncertain, treatment is currently directed against various components of the chronic inflammatory process rather than the cause.[31]

The goals of therapy of RA are

(i) relief of pain

(ii) reduction of inflammation

(iii) protection of articular structures

(iv) maintenance of function

(v) control of systemic involvement[2].

Drug therapy of RA: [31]

First-line therapy anti inflammatories:

- Aspirin
- Nonsteroidal anti-inflammatory drugs
- Cox 2 selective therapies

Second line antirheumatic therapy: (that modify the course of the disease)

- Antimalarials (chloroquin and hydroxyl chloroquin)
- Sulfasalazine
- Methotrexate
- Gold salts (Auranofin, parenteral gold)
- Leflunomide

- TNF inhibitors (Adalimumab,Etanercept,Infliximab)
- Cyclosporin A
- D Penicillamine
- Azathioprine
- Mechanical interventions
- Extracorporeal protein A immunoadsorption column
- Combination therapies

Corticosteroids

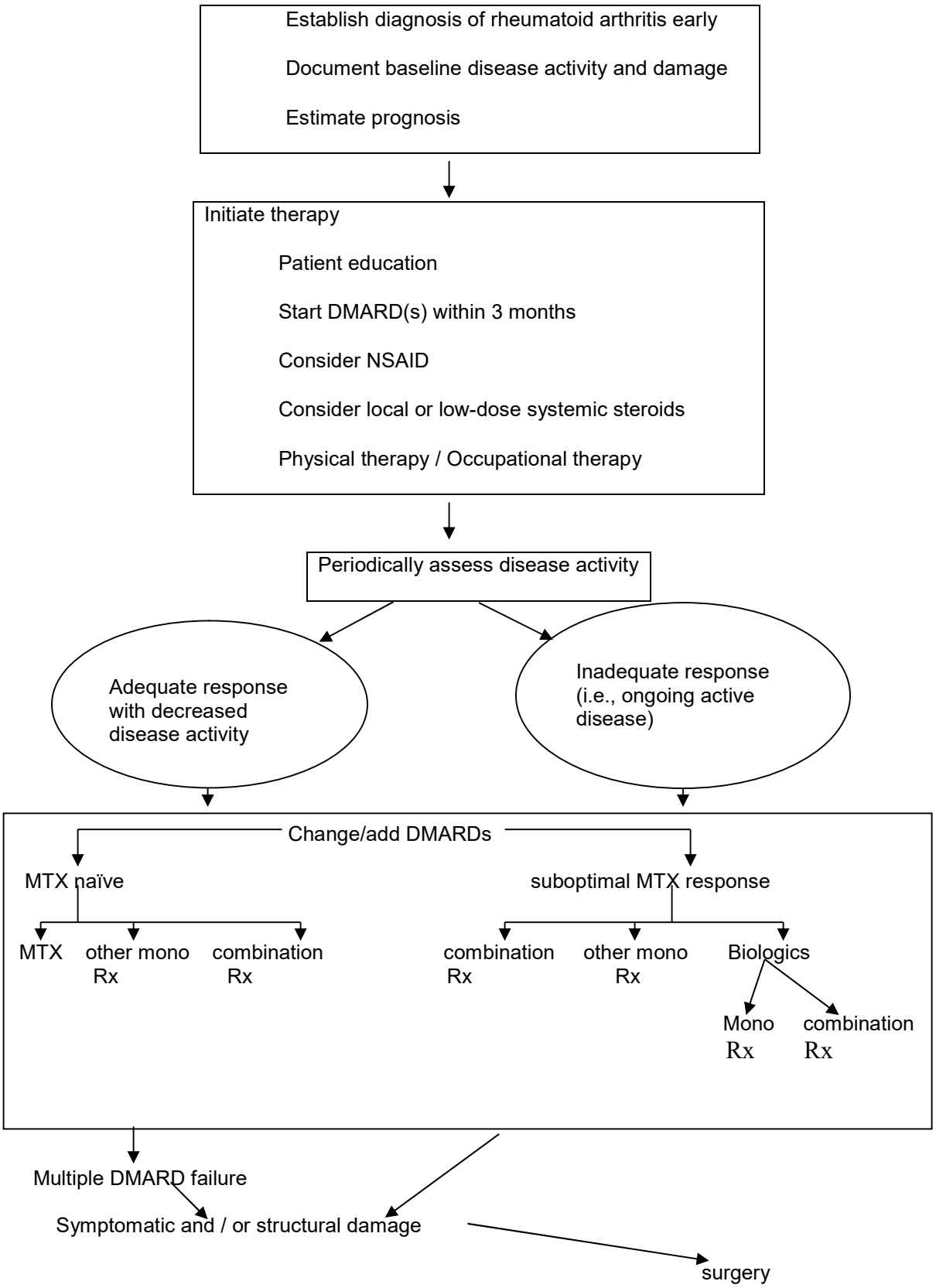
- Systemic steroids (low dose oral and parenteral pulse steroids)

  Intra articular

Investigational agents

- Dietary supplementation (fish oil& plant seed oil)
- Synthetic immunosuppressives (mycophenolate mofetil, FK 506,Fludarabine)
- Tetracycline therapy (minocycline)
- Oral tolerance therapy
- Metalloproteinase inhibitors
- Stem cell transplantation
- Biologic agents (cytokine inhibitors, IL antagonists, TNF monoclonal antibodies, Adhesion molecule antisense ICAM-1, vaccination approaches- T cell receptor peptides).

ACR treatment algorithm [32]



NSAIDS: The standard approach in the treatment of RA continues to be symptomatic treatment of inflammation.[31]They offer reliable but limited symptomatic relief from pain and stiffness. In addition to inhibition of cycloxygenase, they also suppress neutrophil function and in vivo motility. NSAIDs block the activity of the Cox enzyme and therefore production of prostaglandins, prostacyclin and thrombaxanes. They have analgesic, anti-inflammatory and antipyretic properties.[2] Aspirin was until recently the preferred first line NSAID, based on unsurpassed effectiveness and low price. However, a number of trials have shown it to be less well tolerated than other NSAIDs and thus it is no longer considered a first choice. Indomethacin administered at night is popular, due to its combined analgesic and sedative effect.[33] There is no superior NSAID in the treatment of RA. The choice of an NSAID is influenced by the physician's prior experience and by patient preference.[31] NSAIDs alone will not prevent joint erosions and some rheumatologists advocate early combination therapy with slow acting agents.[34]

ADR: Gastric irritation, azotemia, platelet dysfunction and exacerbation of allergic rhinitis and asthma, are related to the inhibition of cycloxygenase activity. The use of coxibs is associated with sodium retention, hypertension and peripheral edema in a fraction of patients, and the use of some coxibs may be associated with an increased incidence of myocardial infarction.[2]

Methotrexate (MTX): Methotrexate is now considered the DMARD of first choice to treat rheumatoid arthritis and is used in up to 60% of patients.

M.O.A: Its mechanism of action at the low doses used in the rheumatic disease probably relates to inhibition of aminoimidazole carboxamide ribonucleotide (AICAR) transformylase and thymidilate synthetase with secondary effects on polymorphonucear chemotaxis. There is some effect on dihydrofolate and this is not a principal mechanism of action.[35]

Dosage: Usual initial dose 7.5 mg orally once weekly. Dose can be increased to 25 mg orally once per week. It can be administered by subcutaneous or intramuscular Injection.[36]

ADR: The toxicities of MTX therapy are mainly gastrointestinal, hematologic, pulmonary and hepatic. Stomatitis occurs in 3-10% of patients. The most common hematologic toxicity is thrombocytopenia in 1-3% of patients. Although pulmonary fibrosis and pneumonitis are severe adverse effects, they are rare.[34] Because it is a folic acid antagonist, MTX can induce a folic acid deficiency. This deficiency is thought partly responsible for MTX toxicity, and supplementation with folic acid 1mg per day has been shown to alleviate some adverse effects. Addition of folic acid to MTX regimen for RA does not compromise drug efficacy.[37]

Antimalarials,chloroquin&hydroxychloroquin: The following mechanisms have been proposed. Suppression of T lymphocytes response to mitogens, decreased leukocyte chemo taxis, stabilization of lysozomal enzymes, inhibition of DNA and RNA synthesis, and trapping of free radicals.[35] Chloroquin might be more effective but more toxic than hydroxychloroquin. Clinical response may not occur for 3 to 6 months after initiating therapy.

ADR: The most common side effects include

- Gastrointestinal intolerance, nausea, epigastric discomfort, anorexia and vomiting.
- Corneal deposits and defects in accommodation may occur.
- The most serious ocular toxicity is retinal disease with macular degeneration caused by the deposit of the 4 aminoquinolones in the melanin containing tissue of the eye.

Dose: Chloroquin should not exceed 3 to 4 mg /kg/d and for hydroxy chloroquin 6 to 7.5 mg/kg/d. Routine ophthalmology examination with visual field testing is generally recommended every 6 months.[31]

Sulfasalazine:[35] Sulfasalazine is metabolized to sulfapyridine and 5 amino salicylic acid and it is thought that the sulfapyridine is probably the active moiety when treating rheumatoid arthritis. Approximately 30% of patients using sulfasalazine discontinue the drug because of toxicity. Common adverse effects include nausea, vomiting, headache and rash. Hemolytic anaemia and methemoglobilinemia also occur.

Gold: Once thought to be the “gold standard” for treatment of RA, the popularity of gold therapy has declined in recent years. Dermatological side effects such as skin rash and stomatitis require discontinuation of gold therapy. Renal toxicity manifests as proteinuria and haematuria; hematologic toxicity presents as anemia, leucopenia or thrombocytopenia .[34]

D-Penicillamine: is rarely used today because of toxicity. [35]

Azothioprine: Toxicity includes bone marrow suppression, gastrointestinal disturbances and some increase in infection risk. Lymphomas may be increased with azothioprine use.[35]

Cyclosporine A: The current recommendation is to reserve cyclosporine for patients refractory to or intolerant of other disease modifying antirheumatic drugs.[34]

Leflunomide: Leflunomide undergoes rapid conversion, both in the intestine and in the plasma to its active metabolite, A77-1726. This metabolite inhibits dihydroorotate dehydrogenase, leading to decrease in ribonucleotide synthesis and the arrest of stimulated cells in G1 phase of cell growth. Consequently leflunomide inhibits T cell proliferation and production of auto antibodies by B cells. Diarrhoea or loose bowels occur in approximately 25% of patients. Other adverse effects associated with leflunomide are mild alopecia, weight gain and increased blood pressure.[35]

Tumor necrosis factor inhibitors:

Three inhibitors are in use. Etanercept, infliximab and adalimumab.

Etanercept, a soluble recombinant TNF receptor; FC fusion protein, is administered at a dosage of 25 mg subcutaneously twice weekly or 50 mg once per week.

Infliximab, a chimeric monoclonal antibody, is administered at a dosage of 3-10mg/kg intravenously initially and then repeated after 2,6,10 and 14 weeks.

Adalimumab, a recombinant monoclonal antibody that binds to TNF receptor sites, and given at a dosage of 40 mg subcutaneously every other week.

ADR: increased risk of certain opportunistic infections, such as tuberculosis. TNF inhibitors should be used with extreme caution in patients with congested heart failure. Infliximab can rarely cause anaphylaxis and induce antiDNA antibodies. A final concern about TNF inhibitors is the expense.[36]

Anakinra: A recombinant form of human IL-1 receptor antagonist. It can be used alone or in combination with DMARDs other than TNF α blocking agents.

ADR: Increased incidence of serious infection.[36]

Many patients continue to have active disease despite intensive DMARD therapy, or experience adverse events. Therefore changes to therapeutic regimens are frequently required during the chronic course of RA, and many patients receive a large number of sequential DMARD courses.[38, 39]

However, the spectrum of traditional DMARDs used in RA is limited. Although the introduction of biological agents has expanded our potential to control RA effectively, even these new agents have only limited efficacy in many patients.[40-43]

Rheumatoid arthritis is associated with accelerated vascular risk with attendant early mortality and excess morbidity.[44] Statins not only inhibit HMG Co A reductase activity, but may also suppress leukocyte-cytokine release, adhesion molecule expression, lymphocyte cognate interactions, and apoptosis in smooth muscle and endothelial cells and alter vascular and neovascularisation functions. These actions have the potential to modify chronic inflammatory response in the vascular and other organ systems.[45]

REVIEW OF THE STUDY DRUG:

STATINS:

These drugs are competitive inhibitors of 3-hydroxy-3-methylglutaryl co enzyme A (HMG-co A) 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.[46]

MOA: [46]

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

Kinetics:

All have high first pass extraction 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.[47]

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.[46]

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. [46]

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.[46]

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.[48] Pleiotropic effects are defined as producing or having multiple effects from a single gene.[49]

Pleiotropic effects of statins: [50]

- ❖ 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,10-80 mg/d; Fluvastatin,20-40mg/d; Lovastatin,10- 80mg/d; Pravastatin, 10- 40mg/d; Rosuvastatin,5-40mg/d; and Simvastatin 5-40mg/d.[46]

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.[46]

Therapeutic indications of statins: [51]

- A series of clinical trials has demonstrated the efficacy of HMG-CO –A 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.[50]

Myopathy:[46] 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: [52]

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

In addition to myalgic complaints, patients with HMGRI- related myopathy may have CK 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).[52]

Rhabdomyolysis: It is a serious muscle damage with CK levels more than 10 times the upper limit of normal. Rhabdomyolysis results in the release of myoglobin into the blood stream, causing possible damage to the kidneys and other organs.[53]

Symptoms: generalized or specific myalgia, muscle tenderness, fever, nausea, vomiting and dark urine.[52]

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.[54]

Mechanism for the adverse effects on muscle:[53]

Figure: 1

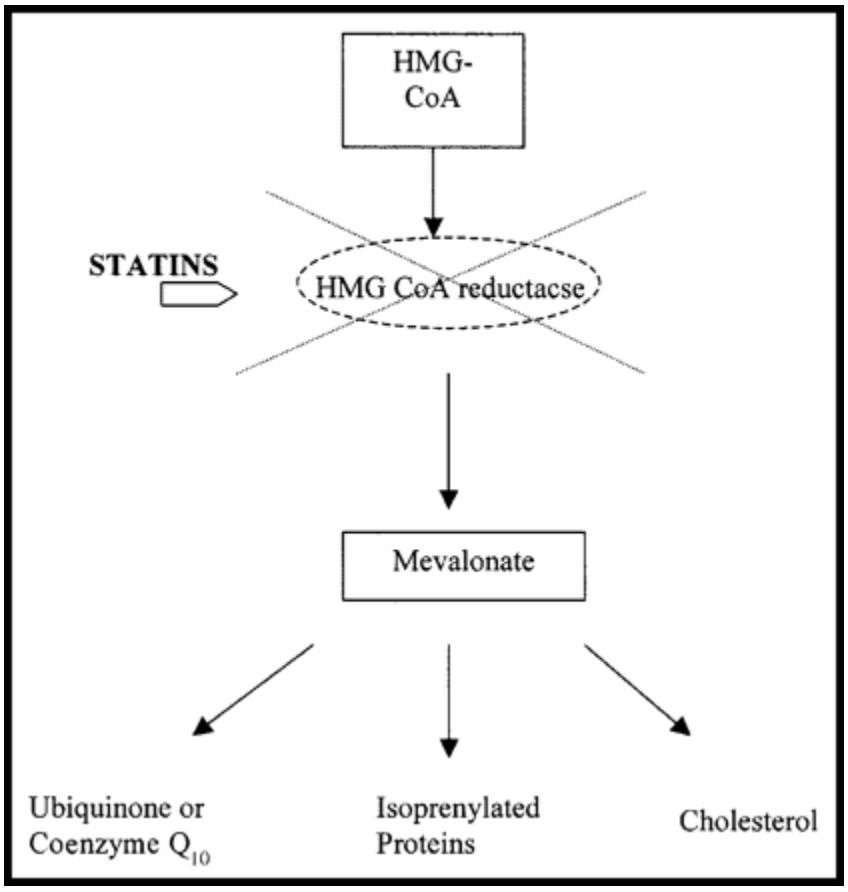


Figure 1 shows the mechanism of action of statins.

Because statins inhibit the production of mevalonate, a precursor of Co Q 10 the synthesis of CoQ_{10} also may be inhibited.[52] 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.[55] There is some evidence to indicate that statin use can exacerbate the normal CK elevations seen after exercise.[54] Since myopathy rarely occurs in the absence of combination therapy, routine CK monitoring is not recommended unless statins are used with one of the predisposing drugs.[46]

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.[57]
- 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.[58]
- 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.[59]

- Macrophage chemokine release, chemotactic responses and oxidative burst are reduced by statins, as is NK cell cytotoxicity in vitro.[59] Antineutrophil cytoplasmic antibody induced neutrophil activation is also suppressed in vitro.[60] Together these effects suggest that innate immune responses may be susceptible to inhibition of HMG-CoA reductase. Similarly, effects on acquired immune responses have emerged. Statins suppress antigen presenting cell major histocompatability complex II expression, T cell –macrophage interactions through leukocyte function antigen-1/ intercellular adhesion molecule -1(LFA-1/ICAM-1) ,T cell 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. Synovial inflammation in RA similarly characterized by activated components of both innate and acquired immune responses. RA synovitis contains a predominant Th1 response, widespread macrophage, fibroblast, mast cell, and B cell activation that in turn generate high autoantibody production (for example, anti CCP, rheumatoid factors) and cytokine release (for example, tumour necrosis factor α (TNF α),IL 1β,IL 6,IL 15 and IL18). Endothelial cell activation, up regulated adhesion molecule expression, and angiogenesis are increasingly recognized. Thus numerous postulated effects for statins might operate within the synovial membrane.[59]

ATORVASTATIN [46]

- Synthetic compound.
- Uptake is mediated by the organic anion transporter 2
- Half life is 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 HMG Co A reductase inhibitors.[61] 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.[62] Atorvastatin reduces LDL-C dependently across 10-80 mg dose range (35.7%-52.2%).[63] 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.[64]

Recent reports have highlighted the shared pathobiology of cardiovascular disease and RA, both of which represent inflammatory disorders. Although

further study is warranted, preliminary investigations also suggest that aggressive anti inflammatory therapy including the adjunctive use of statins, may play important cardio protective role in RA.[65]

A randomized double blind placebo controlled trial of atorvastatin in rheumatoid (TARA) arthritis was conducted in centre for Rheumatic diseases & Department of clinical Biochemistry Glasgow Royal Informatory, Glasgow, United Kingdom. A total of 116 patients with active rheumatoid arthritis were enrolled and randomized by computer to receive atorvastatin 40 mg daily or placebo daily as adjunct to disease modifying therapy. The authors concluded that the data show that statins have a modest anti inflammatory effect and a positive impact on vascular risk.[13]

In the TARA trial conducted in UK, daily dose of 40mg of atorvastatin for 6 months was used without any adverse effects. As our Rheumatologists advised the maximum dose of 20 mg, we had planned our study to find out the efficacy and tolerability of 5mg, 10mg and 20 mg of atorvastatin in our population with RA.

OBJECTIVES

OBJECTIVES

- To assess the beneficial effects of atorvastatin in different doses as an add on therapy to the standard regimen in active rheumatoid arthritis.
- To find out the minimum effective dose of atorvastatin in rheumatoid arthritis.
- To evaluate the tolerability of atorvastatin.

METHODOLOGY

METHODOLOGY

STUDY DESIGN: Open label, randomized comparative, parallel group prospective study.

STUDY CENTRE: Department of Rheumatology,
Govt. General Hospital,
Chennai.

STUDY PERIOD: May 2006 to August 2007

STUDY DURATION: 6 months for every patient

STUDY POPULATION:

Patients attending Rheumatology Out Patient Department with active rheumatoid arthritis.

STUDY SAMPLE: 80 Patients

INCLUSION CRITERIA:

- Age 18 – 60 years
- Both genders.
- Active rheumatoid arthritis in spite of taking standard regimen for more than 6 months (Active rheumatoid arthritis- at least six swollen joints accompanied by two of the following; six tender joints, early morning stiffness lasting at least 30 minutes, and having ESR of at least 28 mm/hr)
- Rheumatoid factor positive
- Disease activity score > 6

- C- reactive protein positive (≥ 6 mg/ lit.)

EXCLUSION CRITERIA:

- Patients with BMI less than 18
- Pregnant and lactating women.
- Patients with diabetes mellitus
- Patients with the history of renal disorders, liver diseases, hypercholesterolemia and hypothyroidism.
- Patients who have undergone any surgery within 3 months.
- Patients who are taking prednisolone > 10 mg /day
- Patients already taking lipid lowering drugs
- Patients who are on amiodarone, digoxin, warfarin, cyclosporine, macrolide antibiotics, azole antifungals, nefazodone, protease inhibitors.
- Patients who are not willing to give informed consent

ASSESSMENT OF EFFICACY:

The improvement in the disease condition is assessed by

- **Disease activity score 28 (DAS 28):** DAS is a combined index that has been developed in Nijmegen in eighties to measure the disease activity in rheumatoid arthritis patients. In order to calculate the DAS28, the following informations are needed.

- ✓ The number of swollen joints
- ✓ The number of tender joints
- ✓ The erythrocyte sedimentation rate measured in mm/hr
- ✓ Patients general health or global disease activity measured on a Visual Analogue Scale (VAS) of 100mm

- **C-reactive protein (CRP)**
- **Erythrocyte sedimentation rate (ESR**)

STUDY PROCEDURE:

ETHICAL CONSIDERATION:

The study was commenced after obtaining approval from the Institutional Ethical committee. Patients with active rheumatoid arthritis attending the rheumatology OPD, Government General Hospital, Chennai, who were already on standard treatment for rheumatoid arthritis, 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 in the trial were registered for the study. Detailed medical history & demographic data were obtained from all the patients who gave informed consent for the study. Following parameters were recorded.

- Body mass index
- Blood pressure
- Detailed clinical examination
- Swollen joint count
- Tender joint count
- Visual analogue pain score obtained from the patient
- Baseline laboratory investigations.

Swollen and tender joint counts:

The joints to calculate DAS 28 include proximal interphalangeal joints, metacarpophalangeal joints, wrist, elbow, shoulder and knee joint on both sides. The swollen and tender joints were counted.

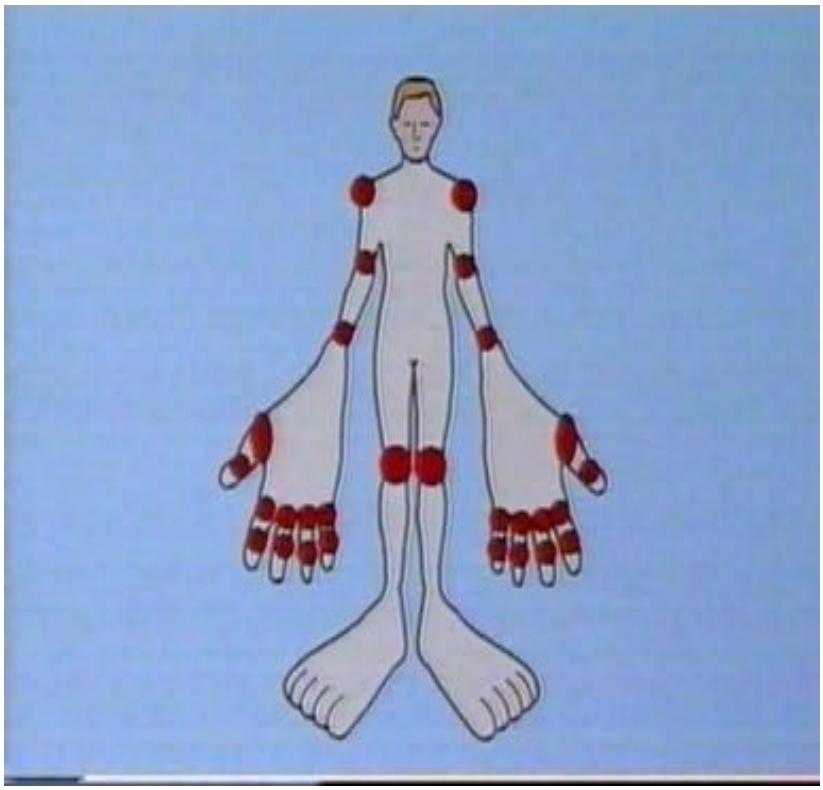
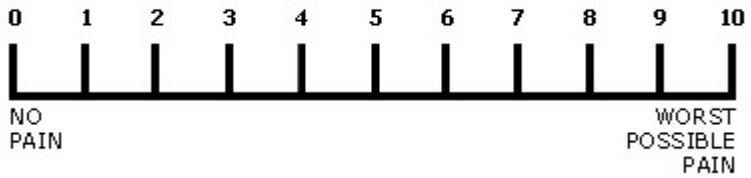


Figure: 2 showing 28 joint count

Patient's Visual Analogue pain Scale: (VAS)



Patients were asked to assess their pain on their own and mark on this scale. The patients were asked to come with empty stomach on the next morning at 8 A.M. for baseline laboratory investigations.

Baseline investigations:

- Complete hemogram (total WBC count, differential count, Platelet count and Hemoglobin)
- ESR
- Rheumatoid factor
- Blood sugar
- Lipid profile
- Serum creatinine
- Serum glutamic oxaloacetic transaminase (SGOT)
- Serum glutamic pyruvic transaminase (SGPT)
- Serum creatine phosphokinase (CPK)
- C-reactive protein (CRP)

RECRUITMENT:

Among 221 patients screened, 80 patients who fulfilled the inclusion criteria were recruited for the study. They were randomly allocated into 4 groups (A, B, C& D) each containing 20 patients by simple randomization method.

Treatment schedule:

Group A (standard treatment) (n = 20)

- Tablet Methotrexate10 mg weekly once on the same day of every week.
- Tablet Folic acid 5 mg weekly once.
- Tablet Prednisolone 5mg daily in the morning after food.
- Tablet Diclofenac sodium 50 mg twice daily after food.
- Tablet calcium 1gm once daily.

Group B (n = 20)

Standard treatment + Atorvastatin 5mg daily at night.

Group C (n = 20)

Standard treatment + Atorvastatin 10 mg daily at night

Group D (n = 20)

Standard treatment + Atorvastatin 20 mg daily at night.

Visits to receive drugs:

Drugs were issued for 2 weeks only. On the15th day, they were asked to return the empty packs (to check the compliance) and receive the drugs for the subsequent 2 weeks. Clear instruction was given to the patients to come to the OPD every 15^{th} day to receive the drug .The same procedure was followed for 6

months. 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:

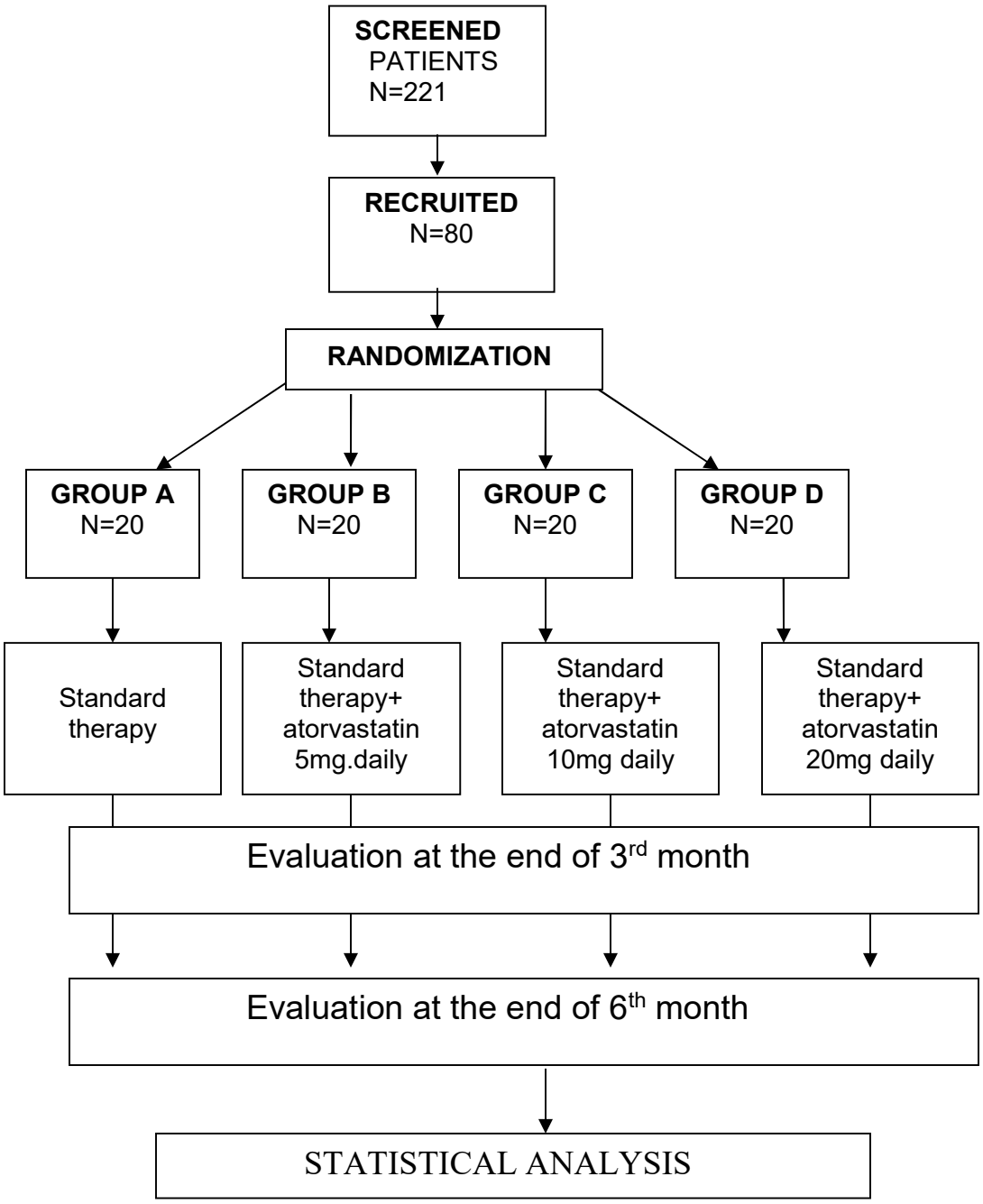
- Follow up visit 1 (at the end of 3rd month)
- Follow up visit 2 (at the end of 6th month)

The following parameters were recorded at the end of 3rd and 6th month.

- ✓ Swollen joint count
- ✓ Tender joint count
- ✓ Visual analogue pain scale (VAS)
- ✓ Laboratory investigations
  - Complete hemogram
  - ESR
  - CRP
  - Serum CPK
  - SGOT
  - SGPT
  - Serum Creatinine
  - Blood sugar
  - Lipid profile

DAS 28 was calculated at the baseline and at the end of 3rd and 6th month by using software DASculator. Statistical analysis was done with one way ANOVA and multiple comparisons with Bonferroni T test.

STUDY PROCEDURE FLOW CHART



RESULTS

RESULTS

The study was taken up to assess the efficacy and tolerability of atorvastatin in different doses as an add on therapy to standard therapy in reducing disease activity of rheumatoid arthritis.

Out of 221 patients screened, 83 patients were found to have hypercholesterolemia, 12 patients had diabetes mellitus, 18 patients were CRP negative, 9 patients had elevated liver enzymes, 19 patients had their ESR < 28 mm and 2 patients had increased serum creatinine levels. They were excluded from the study. 80 patients who fulfilled the inclusion criteria were recruited for the study. They were randomly allocated into 4 groups (A, B, C& D) each containing 20 patients by simple randomization method. Group A received the standard treatment with tablet methotrexate 10 mg weekly once on the same day of the week, tablet folic acid 5 mg weekly once, tablet diclofenac 50 mg twice daily after food, tablet prednisolone 5mg daily in the morning and tablet calcium 1gm daily at night. Group B, Group C & Group D in addition received atorvastatin 5mg, 10mg, and 20mg once daily respectively. Each patient was under treatment for six months. Clinical and laboratory parameters were assessed at the baseline and at the end of 3^{rd} & 6^{th} month. Only 64 patients (15 in group A, 16 in group B, 16 in group C and 17 in group D) completed the study. Statistical analysis was done with one-way ANOVA and multiple comparisons with Bonferroni T test. Sex distribution was analyzed with chi-square test.

Table: 1 DROP OUTS

Groups	Total No. of patients	NO. of drop outs	No.of patients completed the study
Group A	20	5	15
Group B	20	4	16
Group C	20	4	16
Group D	20	3	17
Total	80	16	64

Reasons for drop outs:

- 5 patients (1 from Group B, 2 from Group C and 2 from Group D) didn't turn up one month after the commencement of the therapy for reasons unknown.
- 7 patients (3 from Group A, 3 from Group B, 1 from Group C) didn't want to continue the treatment after 2 months
- 1 patient in Group A developed flare up of disease and admitted in the hospital and was withdrawn from the study.
- 3 patients were lost to follow up at 3rd month (1 from Group A, 1 from Group C, and 1 from Group D)

Table: 2 AGE DISTRIBUTION

Group	No. of patients	Mean Age + SD	One way ANOVA F-test
Group A	15	43.67± 8.30	F=1.22 P=0.30 Not significant
Group B	16	38.31± 5.40	
Group C	16	39.81± 11.50	
Group D	17	40.41± 5.22	

Figure: 3 AGE DISTRIBUTION

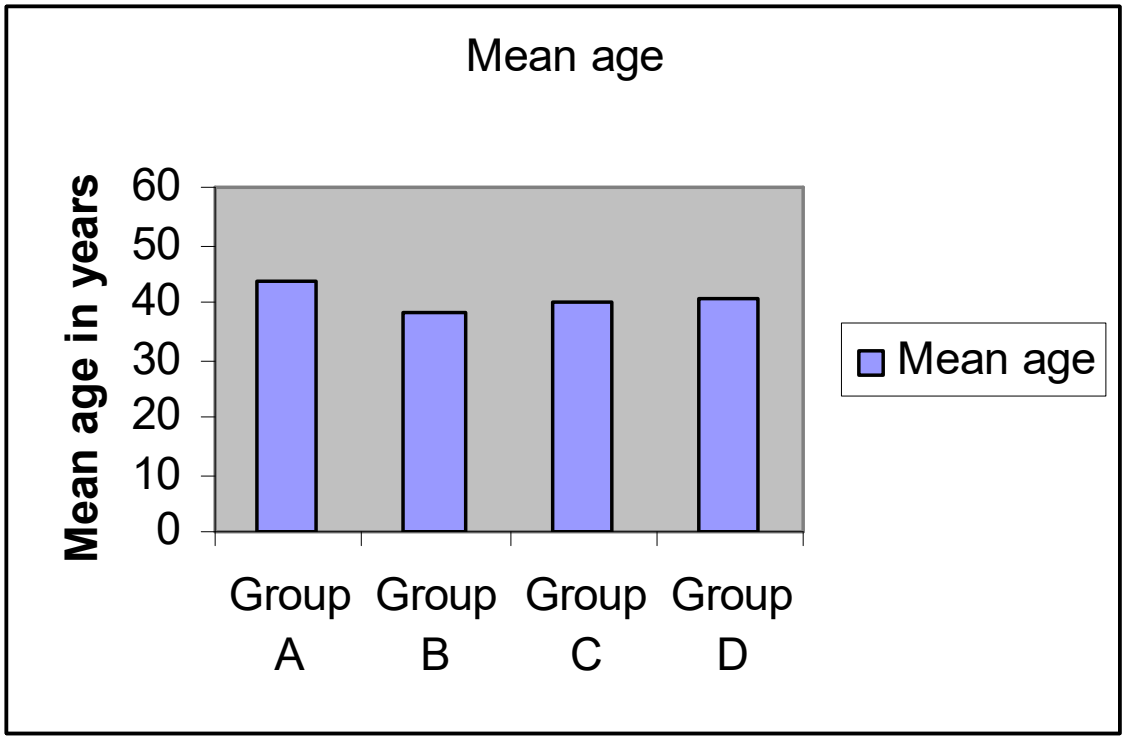


Table: 2 shows that

- The mean age distribution was even in all the study groups.

  There was no significant difference among the study groups.

Figure:3 shows the diagrammatic representation of the mean age distribution in study groups

Table: 3 BODY MASS INDEX

Groups	No. of patients	BMI Mean+SD	One way ANOVA F-test
Group A	15	23.87±1.84	F=1.67 P=0.18 Not significant
Group B	16	22.81±2.42	
Group C	16	22.60±2.62	
Group D	17	24.23±2.88	

Figure: 4 BODY MASS INDEX

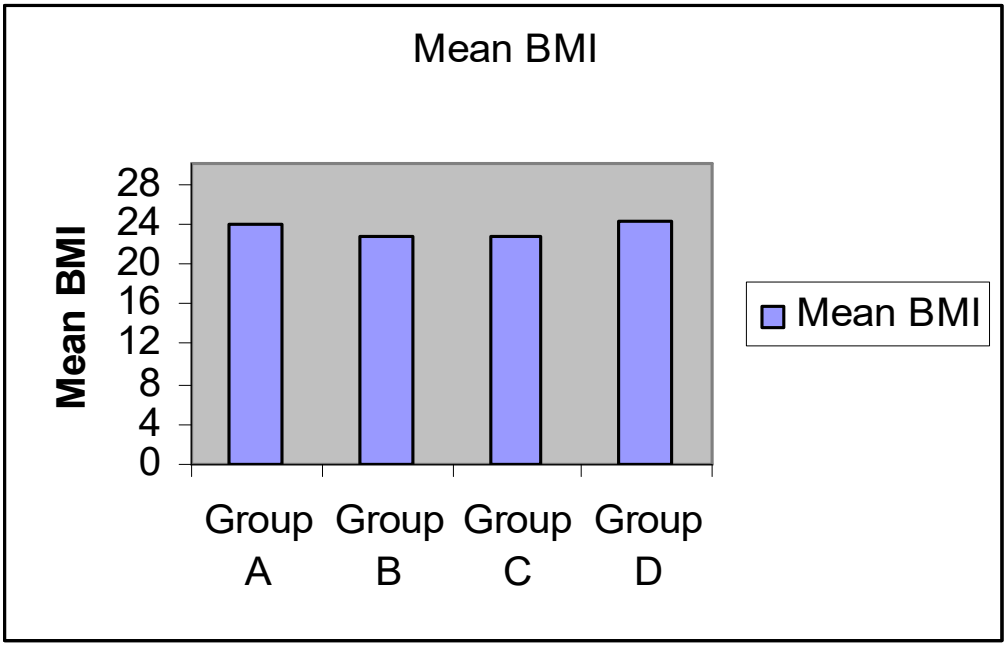


Table: 3 shows the mean body mass index of patients in each study group. There was no significant difference among groups regarding BMI.

Figure:4 shows the diagrammatic representation of the mean BMI of patients in each group.

Table: 4 SEX DISTRIBUTION

Groups	Sex				Chi square test
	Male		Female		
	n	%	n	%	
Group A	1	6.7%	14	93.3%	$\chi 2=0.008$ P=1.00 Not significant
Group B	1	6.3%	15	93.8%	
Group C	1	6.3%	15	93.8%	
Group D	1	5.9%	16	94.1%	

Table: 4 shows the sex distribution in the study groups.

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

Table: 5 COMPARISON OF DAS 28 SCORE

Groups	**Baseline** Mean ± SD	**After 3months** Mean ± SD	**After 6months** Mean±SD	**Oneway ANOVA**
Group A (n = 15)	7.42±0.24	6.9±0.40	6.63±0.32	F=21.707 **P=0.001**
Group B (n = 16)	7.43±0.27	6.5±0.21	6.39±0.48	F=45.472 **P=0.001**
Group C (n = 16)	7.31±0.23	6.23±0.68	4.70±0.45	F=115.258 **P=0.001**
Group D (n=17)	7.44±0.23	4.33±0.19	3.00±0.32	F= 1411.48 **P=0.001**
ONEWAY ANOVA F-TEST	F=0.98 P=0.40 Not Significant	F=121.63 **P=0.001**	F=291.28 **P=0.001**	
BONFERRONI T-TEST		**A** Vs. **C, D**	**A** Vs. **C, D**	

Table: 6 PERCENTAGE REDUCTION IN DAS 28

Groups	**%Reduction of DAS28 After3 months**	**%Reduction of DAS28 After 6 months**
Group A	7.00	10.65
Group B	12.51	14.00
Group C	14.71	35.70
Group D	41.8	59.68

Figure: 5 **COMPARISON OF DAS 28 SCORE**

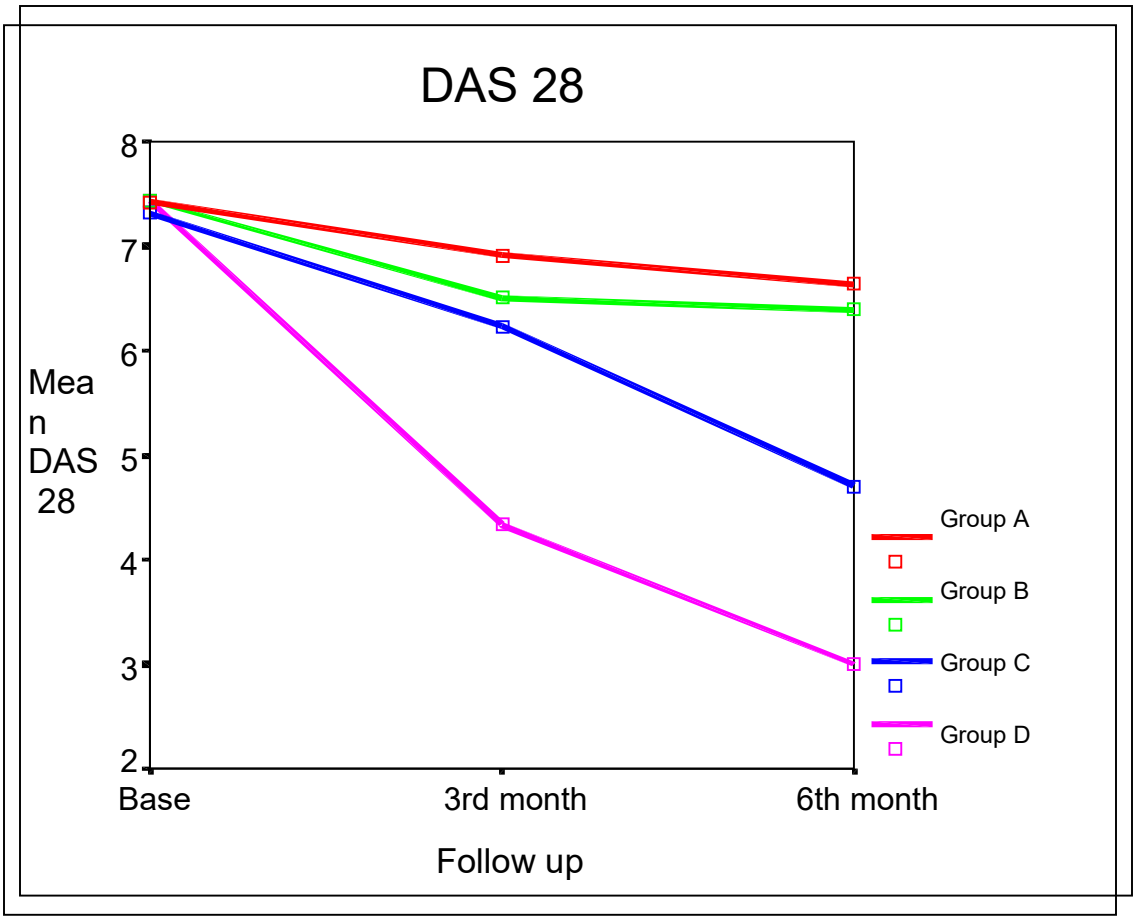


Table: 5 shows the mean DAS 28 scores in each group at baseline, at the end of 3rd month and 6th month.

- At the baseline there was no significant statistical difference among Groups.
- At the end of 3rd month there was a significant statistical difference in Group C & Group D when compared with Group A (P=0.001).
- At the end of 6th month there was a significant statistical difference in Group C & Group D when compared with Group A. (P=0.001)

Table: 6 shows the percentage reduction of DAS 28 in each group after 3rdand 6th month. There was a significant reduction in DAS 28 score in all the study groups at the end of 3rd and 6th month when compared to baseline. The percentage reduction was highest in Group D when compared to other groups.

Figure:5 shows the diagrammatic representation of the DAS 28 score in all the study groups at base line, at the end of 3rd month and 6th month.

Table: 7 COMPARISON OF SERUM CRP

GROUPS	**BASELINE** Mean ± SD	**AFTER 3MONTHS** Mean ± SD	**AFTER 6MONTHS** Mean±SD	ONE WAY ANOVA F-TEST
Group A (n = 15)	35.20±12.39	31.20±12.67	24.80±13.20	F=2.537 P=0.091
Group B (n = 16)	36.00±12.39	21.75±9.00	21.00±12.00	F=9.057 **P=0.001**
Group C (n = 16)	37.50±12.30	14.63±7.89	5.63±4.08	F=56.333 **P=0.001**
Group D (n=17)	35.29±12.35	7.41±5.42	1.76±2.82	F=86.594 **P=0.001**
ONEWAY ANOVA F- TEST	F=0.12 P=0.95 not significant	F=20.22 **P=0.001**	F=24.63 **P=0.001**	
BONFERRONI T-TEST		**A** Vs. **B,C, D**	**A** Vs. **C, D**	

Table: 8 PERCENTAGE REDUCTION IN CRP

Groups	**% Reduction of CRP after 3 months**	**% Reduction of CRP after 6 months**
Group A	11.36	29.55
Group B	39.58	41.67
Group C	60.99	84.99
Group D	79.00	95.01

Figure: 6 COMPARISON OF SERUM CRP

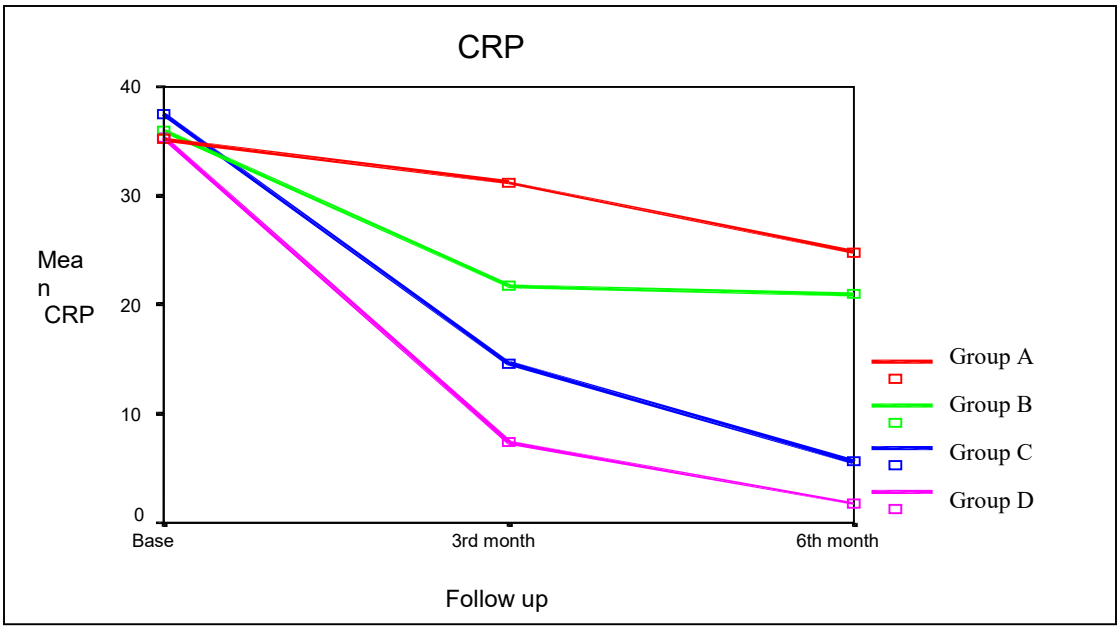


Table: 7 shows the mean C-reactive protein values at baseline, at the end of 3rd month and 6th month.

- At the baseline there was no statistically significant difference among groups.
- At the end of 3rd month, statistical analysis shows significant difference in Group B, Group C & Group D when compared with Group A (P=0.001) .
- At the end of 6th month there was a significant difference in Group C & Group D when compared to Group A (P=0.001).

Table: 8 shows the percentage reduction of CRP in each group after 3rd and 6th month.

Figure:6 shows the diagrammatic representation of C-reactive protein levels in all the study groups at baseline, at the end of 3rd month and 6th month. The reduction in CRP was maximum in Group D and moderate in Group C.

Table:9 COMPARISON OF ESR

GROUPS	**BASELINE** Mean ± SD	**AFTER 3MONTHS** Mean ± SD	**AFTER 6 MONTHS** Mean±SD	ONEWAY ANOVA F-TEST
Group A (n = 15)	77.56±13.87	72.50±15.10	63.25±14.37	F= 3.812 **P = 0.03**
Group B (n = 16)	77.93±13.77	69.60±12.97	59.60±15.60	F=5.766 **P=0.006**
Group C (n= 16)	78.25±13.21	57.44±8.79	38.06±6.68	F= 2.766 **P =0.001**
Group D (n=17)	76.35±13.95	42.82±9.75	25.06±6.63	F=103.73 **P= 0.001**
ONEWAY ANOVA F TEST	F= 0.06 P= 0.98 not significant	F=21.43 **P=0.001**	F=40.43 **P=0.001**	
BONFERRONI T-TEST		**A** Vs. **C, D**	**A** Vs. **C, D**	

Table: 10 PERCENTAGE REDUCTION IN ESR

Groups	**% reduction of ESR after 3 months**	**% reduction of ESR after 6 months**
Group A	6.52	18.45
Group B	10.69	23.52
Group C	26.59	51.36
Group D	43.92	67.18

Figure:7 COMPARISON OF ESR

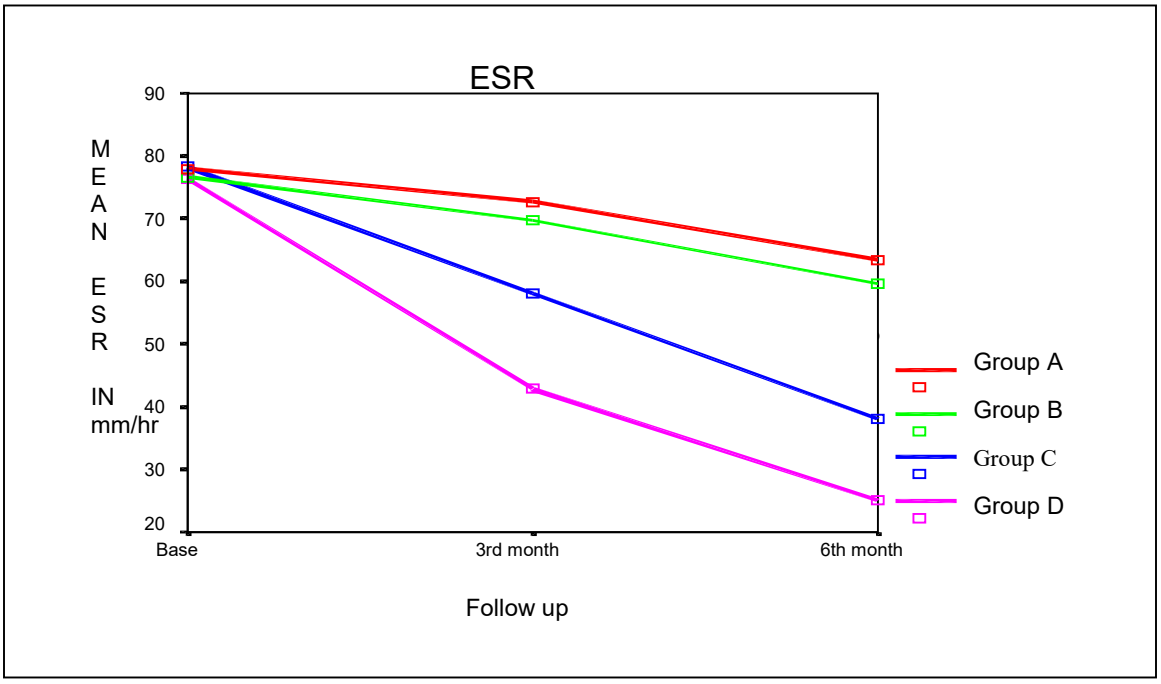


Table: 9 shows the mean ESR values at baseline, at the end of 3rd and 6th month.

- At the baseline there was no significant statistical difference.
- At the end of 3rd month there was a significant statistical difference in Group C & Group D when compared to Group A (P=0.001).
- At the end of 6th month there was a significant statistical difference in Group C & Group D when compared to Group A (P=0.001)

Table: 10 shows the percentage reduction of CRP in each group at the end of 3rd and 6th month.

Figure: 7 shows the diagrammatic representation of ESR levels in all the study groups at baseline, at the end of 3rd month and at the end of 6th month. The reduction in ESR was maximum in Group D and moderate in Group C at the end of 3rd and 6th month.

Table: 11 COMPARISONS OF SERUM CHOLESTEROL

GROUPS	BASELINE Mean ± SD	AFTER 3MONTHS Mean ± SD	AFTER 6 MONTHS Mean±SD	ONEWAY ANOVA F-TEST
Group A (n = 15)	203.60±7.53	200.20±25.62	222.93±24.75	F=5.104 P=0.010
Group B (n = 16)	199.50±6.80	192.19±6.78	198.94±34.41	F=0.623 P=0.541
Group C (n= 16)	198.25±26.91	183.56±25.31	162.44±19.32	F=8.952 **P=0.001**
Group D (n= 17)	196.06±18.38	168.06±15.53	149.94±11.24	39.029 **P=0.001**
ONEWAY ANOVA F-TEST	F=0.53 P=0.66 not significant	F=7.87 **P=0.001**	F=31.40 **P=0.001**	
BONFERRONI T- TEST		**A** Vs. **D**	**A** Vs. **B, C, D**	

Table:12 PERCENTAGE CHANGE IN SERUM CHOLESTEROL

Groups	%change in cholesterol After 3 months	%change in cholesterol After 6 months
Group A	1.67 ↓	9.49 ↑
Group B	3.66 ↓	0.28 ↓
Group C	7.41 ↓	18.06 ↓
Group D	14.28 ↓	23.52 ↓

Figure:8 COMPARISON OF SERUM CHOLESTEROL LEVELS

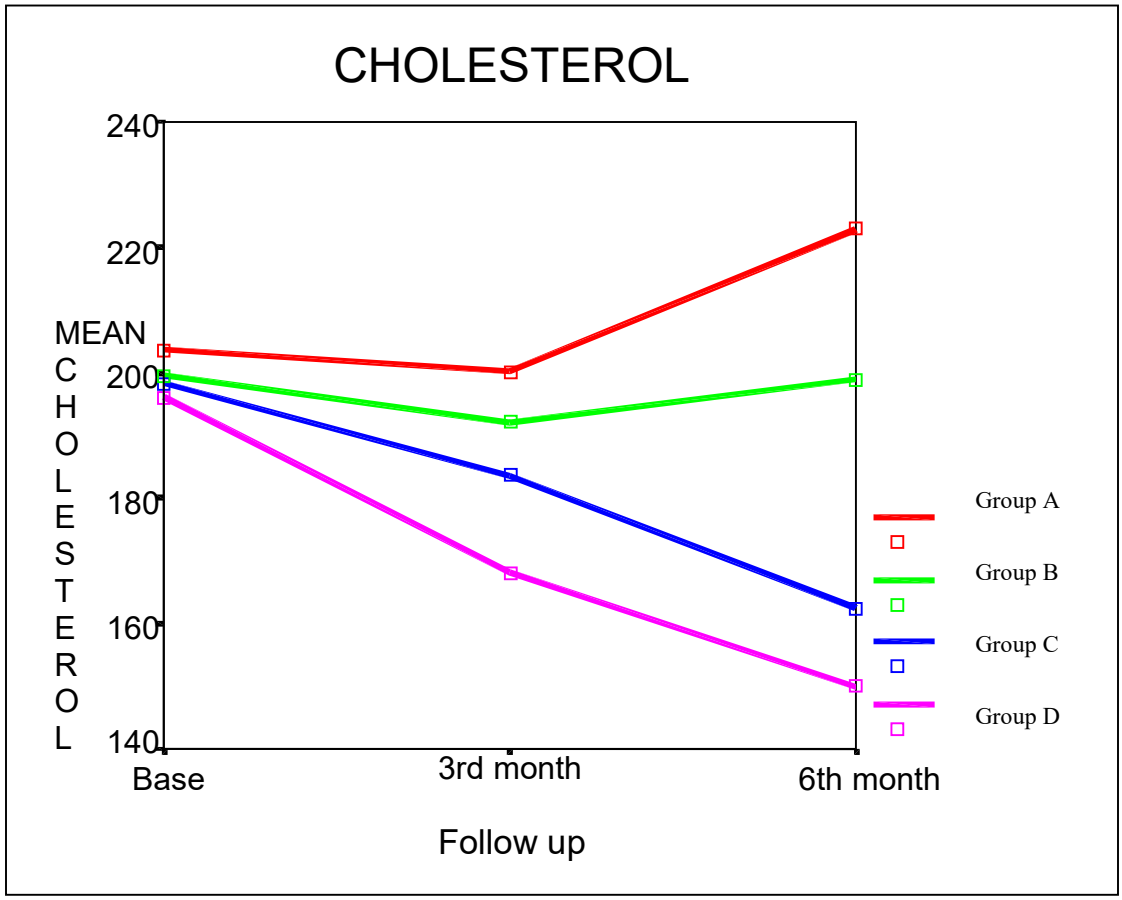


Table :11 shows the mean serum total cholesterol baseline, at the end of 3rd month and 6th month.

- At the baseline there was no significant statistical difference among groups .
- Group A showed a significant increase in total cholesterol level when compared to baseline(P=0.010).
- Group B did not show any significant change in serum cholesterol.
- Group C & Group D showed a significant reduction in total cholesterol levels when compared to baseline(P=0.001).
- At the end of 3rd month there was a significant reduction in total cholesterol in Group D when compared to Group A(P=0.001)
- At the end of 6th month, there was a statistically significant difference in Group B, Group C & Group D when compared to Group A(P=0.001).

Table :12 shows the percentage change in mean serum cholesterol level in each group after 3rd and 6th month. The percentage reduction was higher in Group D.

Figure:8 shows the diagrammatic representation of serum total cholesterol levels in all the study groups at baseline, at the end of 3rd month and at the end of 6th month.

Table: 13 COMPARISON OF SERUM TRIGLYCERIDE

GROUPS	BASELINE Mean + SD	AFTER 3MONTHS Mean + SD	AFTER 6 MONTHS Mean+SD	ONEWAY ANOVA F-TEST
Group A (n = 15)	104.93+4.56	106.27+3.58	121.00+18.52	F=9.500 **P=0.001**
Group B (n = 16)	110.94+9.82	106.56+12.73	108.75+25.10	F=0.259 P=0.773
Group C (n= 16)	106.38+10.65	89.31+9.70	83.06+11.95	F=19.946 **P=0.001**
Group D (n= 17)	106.76+14.89	89.47+17.08	78.47+15.42	F=13.809 **P=0.001**
ONEWAY ANOVA F-TEST	F=0.90 P=0.44 not significant	F=10.66 **P=0.001**	F=19.59 **P=0.001**	
BONFERRONI T-TEST		**A** Vs. **C, D**	**A** Vs. **C, D**	

Table:14 PERCENTAGE CHANGE IN SERUM TRIGLYCERIDE

Groups	%change inTGL after3 months	%change in TGL after 6months
Group A	1.28 ↑	15.31 ↑
Group B	3.95 ↓	1.79 ↓
Group C	16.05 ↓	21.92 ↓
Group D	16.19 ↓	26.50 ↓

Figure:9 COMPARISON OF SERUM TGL LEVELS

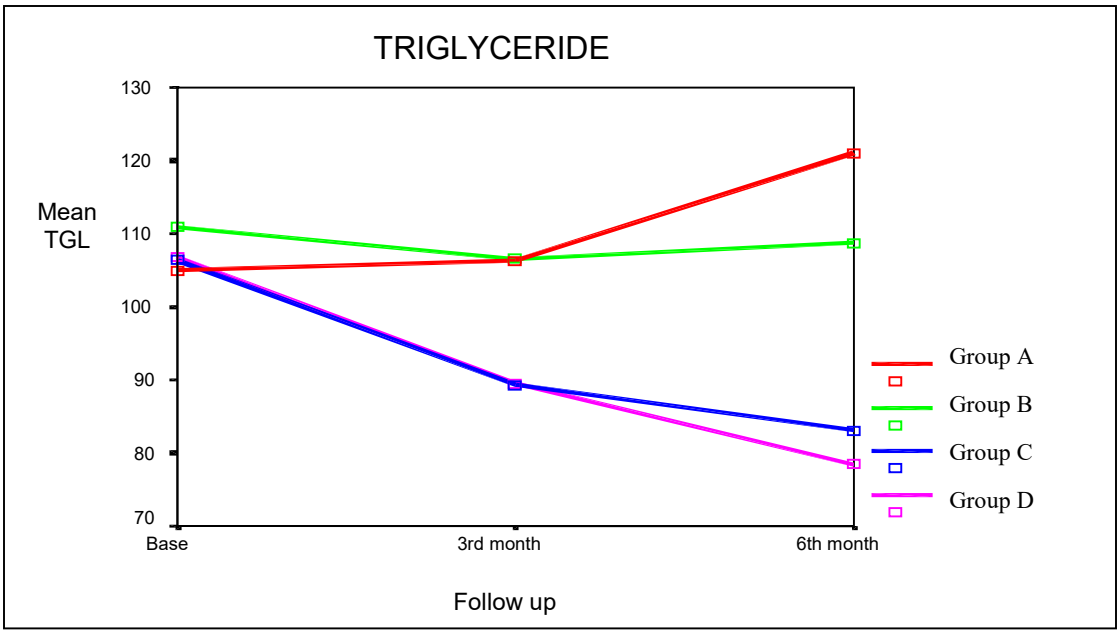


Table: 13 shows the mean serum triglyceride values at baseline, at the end of 3rd month and 6th month.

- At the baseline there was no significant statistical difference among groups.
- There was a significant increase in triglyceride level in Group A when compared to baseline (P=0.001).
- Group B did not show any significant change in serum TGL.
- Group C & Group D showed a significant reduction in serum triglyceride levels when compared to baseline (P=0.001).
- At the end of 3 months there was a significant reduction in Group C & Group D when compared to Group A (P=0.001).
- At the end of 6th month there was a significant reduction in Group C & Group D when compared to Group A (P=0.001).

Table: 14 shows the percentage change in serum TGL level in each group at the end of 3rd and 6th month.

Figure: 9shows the diagrammatic representation of triglyceride levels in all the study groups at baseline, at the end of 3rd month and at the end of 6th month.

Table: 15 COMPARISON OF SERUM LDL LEVELS

GROUPS	**BASELINE** Mean ± SD	**AFTER 3MONTHS** Mean ± SD	**AFTER 6 MONTHS** Mean±SD	ONEWAY ANOVA F-TEST
Group A (n = 15)	139.20±10.60	138.73±9.69	139.67±17.55	F=0.824 P=0.445
Group B (n = 16)	139.81±14.46	145.25±11.78	139.44±11.81	F=3.443 P=0.041
Group C (n = 16)	148.25±7.81	121.44±7.81	102.69±8.88	F=125.34 **P=0.001**
Group D (n = 17)	139.76±10.94	115.06±8.44	104.00±10.30	F=57.601 **P=0.001**
ONEWAY ANOVA F-TEST	F=2.39 P=0.08	F=36.05 **P=0.01**	F=31.42 **P=0.001**	
BONFERRONI T- TEST		**A** Vs. **C,D**	**A** Vs. **C,D**	

Table: 16 PERCENTAGE CHANGE IN SERUM LDL

Groups	**%change in LDL After 3 months**	**%change in LDL After 6 months**
Group A	0.34 % ↓	0.33% ↑
Group B	3.89 % ↑	0.26 ↓
Group C	18.08 % ↓	30.73 ↓
Group D	17.67 ↓	25.59 ↓

Figure: 10 COMPARISON OF SERUM LDL LEVELS

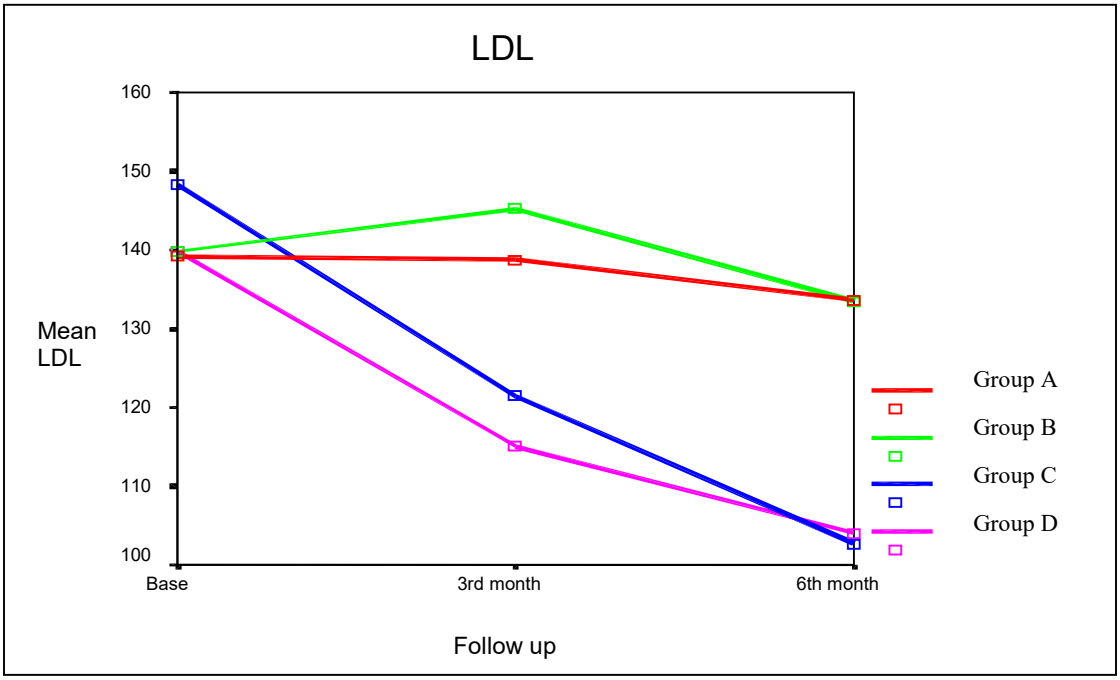


Table: 15 shows the mean serum LDL at baseline, at the end of 3rd month and 6th months

- At the baseline, there was no significant difference among groups.
- Group B showed a significant increase in serum LDL levels when compared to baseline at the end of 3rd month (P=0.041)
- Group C & Group D showed a significant reduction in serum LDL level when compared to baseline (P=0.001).
- At the end of 3rd month Group C & Group D showed a significant reduction in serum LDL level when compared to Group A (P=0.01).
- At the end of 6th month Group C & Group D showed a significant reduction in serum LDL levels when compared to Group A (P=0.001).

Table :16 shows the percentage change in mean serum LDL level in each group after 3rd and 6th month.

Figure 10shows the diagrammatic representation of serum LDL levels in all the study groups at baseline, 3rd month and 6th month.

Table: 17 COMPARISON OF SERUM HDL LEVELS

GROUPS	**BASELINE** Mean ± SD	**AFTER 3MONTHS** Mean ± SD	**AFTER 6 MONTHS** Mean±SD	ONEWAY ANOVA F-TEST
Group A (n = 15)	38.00±5.33	37.80±4.35	37.80±4.78	F=0.009 P=0.991
Group B (n = 16)	38.44±8.69	41.13±8.97	39.81±7.75	F=0.401 P=0.672
Group C (n = 16)	40.56±6.90	43.69±7.40	49.06±6.61	F=6.076 **P=0.005**
Group D (n = 17)	38.35±7.51	46.18±6.38	51.59±5.71	F=17.417 **P=0.001**
ONEWAY ANOVA F-TEST	F=0.41 P=0.75 not significant	F=4.16 **P=0.01**	F=18.41 **P=0.001**	
BONFERRONI T- TEST		**A** Vs. **D**	**A** Vs. **C,D**	

Table: 18 PERCENTAGE CHANGE IN SERUM HDL

Groups	**%change in HDL After 3 months**	**%change in HDL After 6 months**
Group A	0.53 % ↓	0.53% ↓
Group B	7.00 % ↑	3.56 ↑
Group C	7.72 % ↑	20.96 ↑
Group D	20.42 ↑	34.52 ↑

Figure: 11 SERUM HDL LEVELS

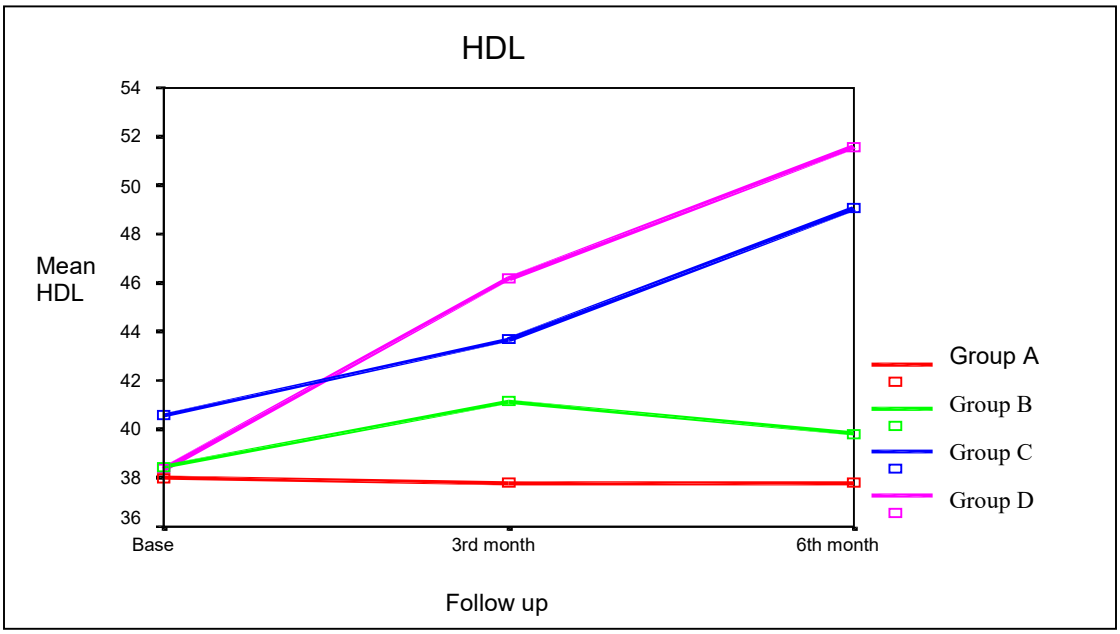


Table 17 shows the mean serum HDL at baseline, at the end of 3rd month and 6th month.

- At the baseline, there was no statistically significant difference among groups.
- There was a significant increase in serum HDL level in Group C (P=0.005) and Group D (P=0.001) when compared to baseline.
- At the end of 3rd month there was a significant increase in serum HDL level in Group D when compared to Group A (P=0.01).
- At the end of 6th month Group C & Group D showed a significant increase in serum HDL level when compared to Group A (P=0.001).

Table 18 shows the percentage change in mean serum HDL level in each group after 3rd and 6th month.

Figure 11shows the diagrammatic representation of serum HDL levels in all the study groups at baseline, at the end of 3rd and at the end of 6th month.

Table: 19 COMPARISON OF SERUM CPK VALUES

GROUPS	**BASELINE** Mean ± SD	**AFTER 3MONTHS** Mean ± SD	**AFTER 6 MONTHS** Mean±SD	ONEWY ANOVA F-TEST
Group A (n = 15)	63.93±28.40	73.40±27.98	71.33±29.24	F=0.456 P=0.637
Group B (n = 16)	55.81±42.58	62.31±33.32	79.31±39.73	F=1.57 P=0.219
Group C (n = 16)	59.06±50.04	98.38±53.00	87.69±31.76	F=3.137 P=0.053
Group D (n = 17)	53.71±32.81	90.47±43.55	92.82±25.06	F=6.815 **P=0.002**
ONEWAY ANOVA F-TEST	F=0.20 P=0.89 not significant	F=2.55 P=0.06	F=1.39 P=0.25	

Table: 19 shows the mean serum CPK values at baseline, at the end of 3rd month and 6th month.

- There was no statistically significant difference in serum CPK levels among groups at baseline.
- There was a significant increase in serum CPK levels (P = 0.002) in Group D when compared to baseline, but values were within normal limits only.

At the end of 3rd and 6th month there was no statistical difference in serum CPK levels among groups.

Table: 20 COMPARISON OF SERUM SGOT VALUES

Groups	Baseline Mean ± SD	After 3months Mean ± SD	After 6 months Mean±SD
Group A (n = 15)	23.67±5.90	24.00±5.72	23.60±3.80
Group B (n = 16)	26.25±7.87	28.06±9.86	28.19±8.44
Group C (n = 16)	20.75±6.06	21.88±6.30	22.50±4.94
Group D (n = 17)	26.71±5.85	24.47±6.62	24.00±7.00
ONEWAY ANOVA F-TEST	F=2.71 P=0.06	F=1.96 P=0.13	F=2.45 P=0.07

Table: 21 COMPARISON OF SERUM SGPT VALUES

GROUPS	**BASELINE** Mean ± SD	**AFTER 3MONTHS** Mean ± SD	**AFTER 6 MONTHS** Mean±SD
Group A (n = 15)	28.07±10.35	31.73±7.90	29.40±6.03
Group B (n = 16)	29.81±6.87	32.31±11.11	32.44±9.42
Group C (n = 16)	23.38±5.68	26.56±7.89	26.13±7.35
Group D (n = 17)	25.12±7.26	30.94±9.28	25.41±8.52
ONEWAY ANOVA F-TEST	F=2.26 P=0.09	F=1.29 P=0.29	F=2.45 P=0.07

Table 20 shows the mean serum SGOT values at baseline, at the end of 3rd month and 6th month.

- There was no statistically significant difference among groups at baseline.
- There was no significant change in serum SGOT level in any of the groups when compared to baseline at the end of 3rd and 6th month.

Table 21 shows the mean serum SGPT values at baseline, at the end of 3rd month and 6th month.

- There was no statistically significant difference among groups at baseline.
- There was no significant change in serum SGPT level in any of the groups when compared to baseline at the end of 3rd and 6th month.

DISCUSSION

DISCUSSION

Rheumatoid arthritis (RA) is a chronic systemic inflammatory illness, affecting approximately 1 % of world's population.[31] The disease is of undetermined etiology involving primarily the synovial membranes and articular structures of multiple joints. The disease is often progressive and results in pain, stiffness and swelling of joints. In late stages, deformity and ankylosis develop. Factors associated with RA include the possibility of infectious triggers, genetic predisposition and autoimmune response. The primary targets of inflammation are synovial membranes and articular structures. Other organs are affected as well.

To date, no cure has been found for RA despite vast global research. Management requires a multidisciplinary approach and focuses primarily on the alleviation of symptoms as well as modification of disease progress to achieve a more favourable outcome for the patient.

Statins are the class of drugs, which act as HMG-CoA reductase inhibitors and are used in the management of hypercholesterolemia. However, the fact that mevalonate is the precursor of isoprenoids that regulate diverse cellular functions, has led investigators to examine the important pleiotropic effects for these agents. Several in vitro and in vivo studies have proved the anti-inflammatory and immunomodulatory properties of statins, especially atorvastatin.

We had taken up this study to evaluate the efficacy and tolerability of atorvastatin in different dosages as an add on therapy to standard therapy.

The age of onset of RA is usually between 25 and 50 years. The disease can occur at any age, but tends to peak in the fourth and fifth decades of life.[66] In our study also the mean age was 43.67, 38.31, 39.81 and 40.41 in Groups A, B, C and D respectively. The distribution of age among the study groups was even and hence there was no statistically significant difference between groups regarding the age.

Literatures say that in RA, female to male ratio is approximately 3:1.[2] In our study, out of 80 patients recruited, only 4 were males and they were equally distributed among four study groups and there was no statistically significant difference among groups. In our study the female to male ratio was 19:1.

DAS 28 score:

Several studies proved the antiinflammatory property of statins. Statins have been suggested to reduce inflammatory cytokine production like tumour necrosis factor alpha, IL 1 beta, IL delta and IL- 6. [7-9] These events are central to RA. Within the rheumatoid synovium the CD4+ cells predominantly differentiate into Th1 like effector cells.[2] Oral atorvastatin produced a shift of Th1 type immune response to Th2 type in a murine model.[10,11] Some cytokines produced by Th2 cells are immunosuppressive, because IL-4 and IL-10 down regulate Th1 cell differentiation.[1] These could be the reasons for the reduction of disease activity with atorvastatin.

In our study when compared to baseline all the study groups showed a significant reduction of disease activity at the end of 3rd month and 6th month

(P= 0.001), but the percentage of reduction of disease activity was higher with atorvastatin 10mg. and highest with 20mg. of atorvastatin. Atorvastatin 20 mg group showed a profound fall in disease activity even at the end of 3rd month (41.8%) itself, when compared to other groups. Hence combining atorvastatin with the standard regimen, the reduction in disease activity will be rapid and quality of life will be improved.

C- reactive protein:

C-reactive protein, an acute phase reactant synthesized in the liver in response to the cytokine IL -6, is also a factor in the development of atherosclerotic plaque. Although CRP was initially believed to be only a marker of vascular inflammation, recent research indicates that it also plays an active role in atherogenesis.[67] There is an association between higher levels of inflammatory markers, such as CRP and the prevalence of myocardial infarction.[68] The most common cause of death in RA is cardiovascular disease, accounting for more than 50% of the mortality.[69] There are studies that support the association of increased CRP and cardiovascular mortality and morbidity.

MIRACL (Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering) study evaluated secondary prevention in patients with history of unstable angina and non-Q- wave acute myocardial infarction. 3086 patients were included in this study and the patients received 80 mg of atorvastatin for 14 weeks. In that study CRP levels were reduced by 83 % after 14 weeks.[70] Similarly, in our study also maximum reduction (95.01%) of CRP was achieved in 20 mg group, followed by 10 mg group (84.99%) after 6 months. So addition of

atorvastatin to the standard therapy for RA will definitely reduce the cardiovascular morbidity and mortality in patients with RA.

ESR;

Erythrocyte sedimentation rate is the most frequently and commonly used laboratory parameter to assess the inflammation or disease activity in RA. Worsening disease is usually associated with an increase in ESR, and remission with normalization of ESR.[21]

In TARA trial with 40 mg of atorvastatin in RA, the percentage of reduction in ESR was 28 %. In our study, even though all the four study groups showed a significant reduction in ESR when compared to baseline values, the percentage reduction was maximum (67.18 %) in 20mg group and moderate (51.36%) in 10 mg group after 6 months.

LIPID PROFILE;

It is important to realize that half of all acute myocardial infarctions occur in patients with normal lipid levels.[71] Systemic inflammation contributes to proatherogenic lipid profiles. In RA, this proatherogenic lipid profile typically includes normal to low levels of total low-density lipoprotein (LDL), but reductions in high-density lipoprotein (HDL) cholesterol as well.[72] Concomitant steroid therapy also may alter the lipid profile. In our study the control group showed a significant increase in total cholesterol after 6 months. (9.49% & ↑ P= 0.01). Glucocorticoids increase serum glucose and thus stimulate insulin release. They stimulate hormone sensitive lipase and produce lipolysis. The

increased insulin secretion stimulates lipogenesis and to a lesser degree inhibits lipolysis, leading to a net increase of fatty acids and glycerol into circulation.[73]

In our study significant reduction in serum total cholesterol levels was achieved in 20 mg group (23.52% after 6 months) followed by atorvastatin 10mg. group (18.06% after 6 months) when compared to baseline. We can attribute this to atorvastatin therapy. Atorvastatin 5mg group showed no significant change.

There was a statistically significant reduction in TGL in group C & D (P=0.001), when compared to baseline. In analyzing the percentage change, group A showed 15.31% increase after 6 months, whereas group C &D showed a very good reduction in TGL (21.92% and 26.50%) respectively.

Atorvastain 20 mg and 10mg significantly reduced LDL-C levels (P=0.001). Atorvastatin 5mg also reduced LDL-C significantly (P=0.04).

Atorvastatin 20mg group followed by atorvastatin 10 mg group showed a very good improvement in HDL –C levels (P=0.001). Atorvastatin 5mg didnot show any significant change in HDL-C levels.

As atorvastatin produced a marked increase in HDL levels and reduction in TGL and LDL-C levels in our study, addition of atorvastatin may reduce the risk of atherosclerosis and also the cardiovascular morbidity and mortality in RA patients.

Every RA patient is maintained with low dose steroids and high dose steroids are given when there is disease flare up. The steroids may be the cause

for the increase in total cholesterol and TGL values. Hence addition of atorvastatin will be more beneficial.

SERUM CPK, SGOT AND SGPT;

There was a significant increase in CPK levels in 20 mg group. But the values were within normal reference range. There was no significant change in SGOT & SGPT in any of the study group when compared to baseline. This is in accordance with TARA trial where there was no significant increase in SGOT, SGPT or CPK levels.[13]

Other laboratory parameters like haemogram didnot show any significant change among groups. Blood sugar and serum creatinine were within normal limits.

ADVERSE EFFECTS;

Three patients (1 from control group, 1 from atorvastatin 5 mg group and 1 from atorvastatin 20 mg group) complained of hair loss, which may be due to methotrexate. No other adverse effect was noted by the patients or observed by the physician.

So in RA patients, addition of atorvastatin 20 mg and 10 mg produced significant improvement in disease activity and significant reductions in CRP and ESR levels when compared to standard therapy given alone. The reduction of elevated CRP levels by atorvastatin may reduce the risk of cardiovascular events independent of the effect of statins on lipid profile in RA. Atorvastatin also produced favourable changes in lipid profile. Atorvastatin 20 mg was more effective than 10 mg and 5mg of atorvastatin was not effective.

Apart from hypolipidemic property, atorvastatin has the disease modifying action in RA. It also reduces CRP. Moreover it prevents the elevation of lipid profile due to the concomitant administration of steroids. Though RA patients respond well to atorvastatin 10mg, atorvastatin 20mg produced a maximum response and it was well tolerated. Hence atorvastatin 20mg. can be recommended as an add on therapy to standard therapy for rheumatoid arthritis.

CONCLUSION

CONCLUSION

Based on the results of our study we conclude that

- Atorvastatin produces beneficial effects in rheumatoid arthritis.
- Atorvastatin 5mg is not effective. Atorvastatin 10mg is effective and atorvastatin 20mg is more effective in reducing the disease activity in rheumatoid arthritis.
- Atorvastatin 20 mg is well tolerated in rheumatoid arthritis.

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BIBILIOGRAPHY

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APPENDIX

APPENDIX 1

ABBREVIATIONS

ADR	**Adverse drug reactions**
CPK	**Creatine Phosphokinase**
CRP	**C-Reactive Protein**
CYP	**Cytochrome P**
DMARD	**Disease modifying antirheumatoid drugs**
ESR	**Erythrocyte sedimentation Rate**
HDL-C	**High density lipoprotein -cholesterol**
HMG-Co A	**3 Hydroxy 3 methyl glutaryl Co enzyme A**
IL	**Interleukin**
LDL-C	**Low density lipoprotein cholesterol**
MOA	**Mechanism of action**
MTX	**Methotrexate**
NK Cells	**Natural killer cells**
RA	**Rheumatoid arthritis**
SGOT	**Serum Glutamic Oxaloacetic Transaminase**
SGPT	**Serum Glutamic Pyruvic Transaminase**
TGF	**Transforming growth factor**
TGL	**Triglycerides**
Th 1 cells	**T helper 1 cells**
Th 2 cells	**T helper 2 cells**
TNF	**Tumour necrosis Factor**

APPENDIX 2

ஒப்புதல் படிவம்

ஆய்வு செய்யப்படும் தலைப்பு :
அட்டர்வாஸ்டாட்டின் என்ற மருந்தினை ருமாட்டாய்டு மூட்டு வாதத்திற்கான நடைமுறையில் உள்ள சிகிச்சை உடன் இணைத்துக் கொடுப்பதால் ஏற்படும் நோயின் வீரியம் குறைதல் பற்றிய ஒரு திறந்தநிலை ஒப்பீட்டு ஆய்வு.

ஆராய்ச்சி மையம் :Klf;Fthjapay; GwNehahspfs; gphpT
அரசு மருத்துவக் கல்லூரி மருத்துவமனை
சென்னை.

பங்கு பெறுவரின் பெயர் :
பங்கு பெறுவரின் வயது :
பங்கு பெறுவரின் எண் :

பங்குபெறுவர் இதனை (✓)குறிக்கவும்

மேலே குறிப்பிட்டுள்ள மருத்துவ ஆய்வின் விவரங்கள் எனக்கு விளக்கப்பட்டது. என்னுடைய சந்தேகங்களைக் கேட்கவும், அதற்கான தகுந்த விளக்கங்களை பெறவும் வாய்ப்பளிக்கப்பட்டுள்ளது என அறிந்து கொண்டேன். ☐

நான் இவ்வாய்வில் தன்னிச்சையாக தான் பங்கேற்கிறேன். எந்த காரணத்தினாலோ எந்த கட்டத்திலும், எந்த சட்ட சிக்கலுக்கும் உட்படாமல் நான் இவ்வாய்வில் இருந்து விலகி கொள்ளலாம் என்றும் அறிந்து கொண்டேன். ☐

இந்த ஆய்வு சம்பந்தமாகவோ, இதை சார்ந்து மேலும் ஆய்வு மேற்கொள்ளும் போதும் இந்த ஆய்வில் பங்குபெறும் மருத்துவர் என்னுடைய மருத்துவ அறிக்கைகளை பார்ப்பதற்கு என் அனுமதி தேவையில்லை என அறிந்து கொள்கிறேன். நான் ஆய்வில் இருந்து விலகிக் கொண்டாலும் இது பொருந்தும் என அறிகிறேன். ☐

இந்த ஆய்வின் மூலம் கிடைக்கும் தகவலையோ, முடிவையோ பயன்படுத்திக் கொள்ள மறுக்கமாட்டேன். ☐

இந்த ஆய்வில் நான் நடைமுறை சிகிச்சை மட்டுமோ அல்லது அட்டர்வாஸ்டாட்டின் 5 மி.கி அல்லது 10 மி.கி அல்லது 20 மி.கி இணைத்தோ 6 மாதங்களுக்கு உட்கொள்ளச் சம்மதிக்கிறேன். ☐

இந்த ஆய்வில் பங்குகொள்ள ஒப்புக்கொள்கிறேன். எனக்கு கொடுக்கப்பட்டுள்ள அறிவுரைகளின்படி நடந்துகொள்வதுடன் இந்த ஆய்வை மேற்கொள்ளும் மருத்துவருக்கு உண்மையுடன் இருப்பேன் என்றும் உறுதி அளிக்கிறேன். என் உடல்நலம் பாதிக்கப்பட்டாலோ அல்லது எதிர்பாராத வழக்கத்திற்கு மாறான நோய்குறி தென்பட்டாலோ உடனே இதை மருத்துவரிடம் தெரிவிப்பேன் என உறுதியளிக்கிறேன். ☐

இந்த ஆய்வு ஆரம்பித்து முடியும் வரை என்னிடமிருந்து 30 மில்லி இரத்தம் எடுக்கப்படும் என்று அறிவிக்கப்பட்டது. ☐

பங்கேற்பவரின் கையொப்பம் ---------- இடம் ---------- தேதி
கட்டைவிரல் ரேகை

பங்கேற்பவரின் பெயர் மற்றும் விலாசம் ----------
ஆய்வாளரின் கையொப்பம் ---------- இடம் ---------- தேதி

ஆய்வாளரின் பெயர் ----------

APPENDIX 3

PATIENT CONSENT FORM

STUDY TITLE:

"A RANDOMISED, OPEN LABEL, COMPARATIVE, PROSPECTIVE, PARALLEL GROUP STUDY OF ATORVASTATIN AS AN ADD ON THERAPY TO STANDARD TREATMENT IN REDUCING DISEASE ACTIVITY OF RHEUMATOID ARTHRITIS"

Study Centre : Department of Rheumatology,Government General Hospital,Chennai.

Patient's Name : _____

Patinet's Age : _____

Identification Number : _____

Patients may check (✓) these Boxes

I confirm that I have understood the purpose and procedure of the above study. I have the opportunity to ask the 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, without my legal rights being affected.	☐
I understand that the investigator, the ethics committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current tsudy 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 identify 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 detorieration in my health or well being or any unexpected or unusual symptoms.	☐
I hereby agree to allow the investigator to take around 30ml of blood from me for the laboratory investigations until the completion of study.	☐
I hereby give permission to undergo complete physical examination, and diagnostic tests including hematological, Biochemical, Radiological and urine examination.	☐

Signature / Thumb Impression of the patient. _____ Place _____ Date

Patient's Name&Address : _____

_____

Signature of the Investigator : _____ Place _____ Date

Study Investigator's Name : _____

APPENDIX 4

CASE RECORD FORM

NAME: **AGE:** **SEX:**

ADDRESS:

PHONE:

HEIGHT: **WEIGHT:** **BMI:**

GROUP:

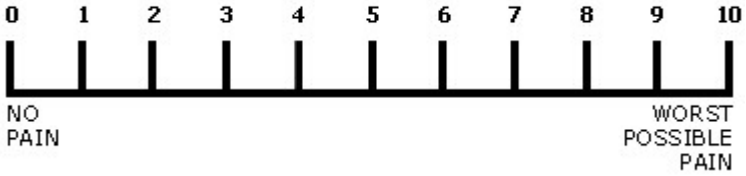
HISTORY:

Clinical and laboratory parameters :

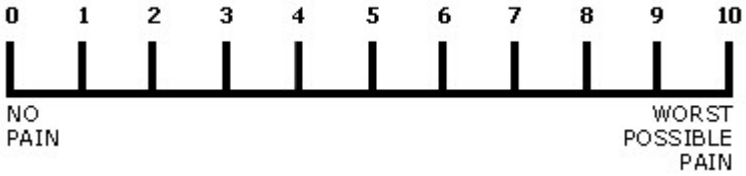
PARAMETERS	BASELINE	AT THE END OF 3RD MONTH	AT THE END OF 6TH MONTH
Swollen joint count			
Tender joint count			
Haemogram			
ESR			
CRP			
Blood sugar			
Serum Creatinine			
Total Cholesterol			
TGL			
LDL			
HDL			
CPK			
SGOT			
SGPT			
DAS 28			

VISUAL ANALOGUE PAIN SCALE

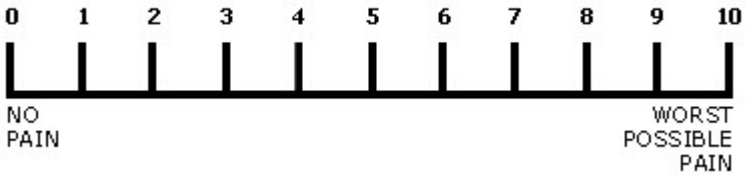
At baseline



At the end of 3rd month



At the end of 6th month



FOLLOW UP: