



## PITAVASTATIN IN THE MANAGEMENT OF RHEUMATOID ARTHRITIS

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### ABSTRACT

Rheumatoid Arthritis (RA) is an auto-immune disease predominately affects synovial joints. The clinical hallmark of RA is inflammation of peripheral joints - typically in the hands (metacarpophalangeal joints and proximal interphalangeal joints), causing pain, stiffness and often some degree of irreversible joint damage, deformity and disability. RA can also affect various organs and organ systems including skin, lungs, heart, kidney, nervous system and gastrointestinal tract. Worldwide prevalence of RA was recorded from the range between 2.0 to 10.7 per 1,000 based on the 1987 revised American College of Rheumatology

(ACR) criteria. In INDIA, the prevalence is found to be approximately 0.75%. Classification as definite RA is based on the joint American College of Rheumatology (ACR) and the European League against Rheumatism (EULAR) criteria. The management of RA involves the use of Symptom modifying anti rheumatoid drugs (SMARDs) like Non steroidal anti-inflammatory drugs, glucocorticoids and Disease modifying anti rheumatoid drugs (DMARDs) like Methotrexate, Sulphasalazine etc. Statins, introduced to the market as lipid-lowering agents, have been shown to reduce cardiovascular morbidity and mortality. Various trials with statins on RA like TARA trial have proved their efficacy in the management and prevention of risk factors in RA. Pitavastatin, the seventh statin is a new member of the statin family. Being a lipophilic statin it can easily penetrate hepatic and extrahepatic tissues like bone and exert its anti-inflammatory effect. It is proved to be efficacious compared to other statins based on Patrol trial, Lives study and Chiba study. Many studies demonstrated that

pitavastatin increases bone resorption in RA. Pitavastatin is proved to be a more safer and efficient adjuvant drug in the management of RA along with DMARDs, particularly in elderly patients.

**KEY WORDS:** Rheumatoid Arthritis, Statins, Pitavastatin, Synovitis, Inflammation.

## INTRODUCTION

### RHEUMATOID ARTHRITIS (RA)

Human body is equipped with a powerful set of tools for resisting invading microorganisms (such as viruses, bacteria and parasites) known as the immune system. Sometimes the system goes twisted and turns against the body itself and begins to destroy healthy tissue. These misdirected immune responses are referred to as autoimmunity and the diseases against are referred as autoimmune diseases.<sup>[1]</sup> Autoimmune diseases affect about five percent of people in developed countries; over 80 of these “auto aggressive” diseases are documented.<sup>[2]</sup> Rheumatoid Arthritis (RA) is one of an auto-immune disease in which body mistakenly considers some parts of its own system as pathogens and attacks them.<sup>[3]</sup> The clinical hallmark of RA is inflammation of peripheral joints - typically in the hands (metacarpophalangeal joints and proximal interphalangeal joints) causing pain, stiffness and often some degree of irreversible joint damage, deformity and disability. Additionally, there is also a significant systemic inflammatory state present that may promote a number of other extra-articular effects including coronary artery disease, pulmonary fibrosis, osteoporosis and vasculitis.<sup>[4]</sup> RA predominately affects synovial joints. Inflammation of the synovium (synovitis) is associated with hyperplasia of synovial cells, excess synovial fluid, and pannus formation. Pannus denotes a thickened membrane-like covering of inflammatory granulation tissue over the articular cartilage.<sup>[5]</sup>

### PREVALENCE OF RA

The prevalence of RA is more common in women and in developed countries.<sup>[6]</sup> Worldwide prevalence of RA range was identified between 2.0 to 10.7 per 1,000 based on the 1987 revised American College of Rheumatology (ACR) criteria.<sup>[7]</sup> In INDIA, the prevalence is found to be approximately 0.75%.<sup>[8]</sup> The irreversible joint damage and systemic complications are associated with substantial morbidity and increased mortality.<sup>[9,10]</sup> Patients with active RA suffer from significant decline in functional capacity. As many as 40% become work disabled within 5 years from onset of symptoms.<sup>[11]</sup> It lessens patient's quality

of life and impairs their ability to work.<sup>[12]</sup> Direct and indirect costs on their life are also more.<sup>[13]</sup>

### **ETIOLOGY AND PATHOPHYSIOLOGY**

The pathophysiology of RA remains uncertain, it appears that B cell lymphocytes and tumour necrosis factor alpha (TNF $\alpha$ ) are important mediators.<sup>[14]</sup> Inflammation can induce bone damage and these two processes are linked via common mediators.<sup>[5]</sup> These mediators involved include

1. Receptor activator of NF- $\kappa$ B ligand (RANKL) and its receptor RANK.
2. Proinflammatory cytokines (e.g., tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ).
3. Interleukins (IL-1, IL-6, IL-17 and IL-18).
4. Matrix degrading enzymes e.g., matrix metalloproteinases (MMPs), Cathepsin K (Cat K).

Antigens are typically presented to T cells by B cells via HLA-DR4. The presence of autoantibodies, such as rheumatoid factor (RF) and anti-citrullinated protein antibody (ACPA) (tested as anti-cyclic citrullinated peptide [anti CCP]), can precede the clinical manifestation of RA by many years.<sup>[7,12,15,16,17,18]</sup> HLA DR3 and DRH genes are associated with a greater frequency of extra-articular diseases. Hematological abnormalities like anemia (normocytic, normochromic), thrombocytopenia, eosinophilia and raised Erythrocyte Sedimentation Rate (ESR) and raised C- Reactive Protein (CRP) are also present in RA patients. The synovitis of RA affects multiple sites causing widespread pain, and the subsequent destruction of the joints leading to severe disability affecting all aspects of motor function from walking to fine movements of the hand.<sup>[19]</sup> RA also affects the lungs, pleura, pericardium, sclera and subcutaneous tissue.<sup>[5]</sup>

### **SYMPTOMS AND DIAGNOSTIC CRITERIA**

The signs and symptoms include pain, swelling, tenderness and warmth around the joint, stiffness particularly in the morning or after a period of rest, poor grip strength, tiredness, irritability depression, flu-like symptoms, loss of weight and rheumatoid nodules – fleshy lumps usually seen on hands, feet and elbows.<sup>[20]</sup> RA Patients may find that their symptoms come and go with little pain, swelling or inflammation. Flare-ups exist for a few days to a couple of months. They probably won't be able to predict when they'll occur.<sup>[20]</sup> RA, is the number one cause of early retirement, disability payments, and loss of employment.<sup>[21]</sup> The social and economic consequences for the individual are drastic even in the first years of the disease. Within seven years, up to 40 percent of patients are no longer able to work in their

profession.<sup>[22]</sup> Ten years after onset of the disease, nearly 60 percent of RA patients are no longer able to work.<sup>[20]</sup>

A joint working group of the American College of Rheumatology (ACR) and the European League against Rheumatism (EULAR) was formed to develop a new approach for classification of RA. In the new criteria set, classification as definite RA is based on the confirmed presence of synovitis in at least 1 joint.<sup>[19]</sup>

The achievement of a total score of at least 6 (of a possible 10) from the individual scores in four domains was determined. The highest score achieved in a given domain is used for this calculation. These domains and their values are

1. Number and site of involved joints

- a) 2 to 10 large joints (from among shoulders, elbows, hips, knees, and ankles) = 1 point.
- b) 1 to 3 small joints (from among the metacarpophalangeal joints, proximal interphalangeal joints, second through fifth metatarsophalangeal joints, thumb interphalangeal joints, and wrists) = 2 points.
- c) 4 to 10 small joints = 3 points.
- d) Greater than 10 joints (including at least 1 small joint) = 5 points.

Early bone loss is evident from decrease in bone mineral density (BMD) in the metacarpal bones and forearm measured by dual X-ray absorptiometry (DXA) and digital X-ray radiogrammetry (DXR) and radiological alterations in patients with early and established RA.<sup>[23]</sup>

2. Serological abnormality (rheumatoid factor or anti- citrullinated peptide/protein antibody)

- a) Low positive (above the upper limit of normal [ULN]) = 2 points.
- b) High positive (greater than three times the ULN) = 3 points.

3. Elevated acute phase response (erythrocyte sedimentation rate [ESR] or C-reactive protein [CRP]) above the ULN = 1 point.

4. Symptom duration atleast six weeks=1point.<sup>[19,24]</sup>

## ASSOCIATION OF RA WITH OTHER CO-MORBIDITIES

**On Bone and joint:** Osteoporosis is more common, due to reduced mobility, inflammation and sometimes may be due to the drugs (particularly steroids). People with RA are more prone to infections than the rest of the population, probably due to abnormalities in the

immune system or because of their medication (the immunosuppressant effects of steroids). Clearly RA has the potential for not only widespread joint and soft tissue damage, but also inflammatory processes that can directly or indirectly affect most organ systems in the body and result in premature death. Appropriate management therefore needs to address not only the impact on joints, but also focus on the whole body, the person suffering from the disease, their families and careers, and their employers.

**Extra-articular manifestations:** RA is a serious condition and patients with extra-articular manifestations should be aggressively treated and monitored.<sup>[25]</sup> Extra-articular manifestations of RA occur in about 40% of patients, either in the beginning or during the course of their disease.<sup>[26]</sup> The extra-articular manifestations of RA can occur at any age after onset. It is characterized by destructive polyarthritis and extra-articular organ involvement, including the skin, eyes, heart, lungs, kidneys, nerves and gastrointestinal tract. **Skin** (20%) - Rheumatoid nodules, Small vessel vasculitis, Splinter haemorrhages, Periungual infarcts, Leg ulcers, Digital gangrene and Painful ulcerations.; **Ocular manifestations** (10%) - Xerostomia in a secondary Sjogren's syndrome, Episcleritis, Scleritis, Peripheral ulcerative keratitis; **Oral manifestations** - Dryness of mouth and salivary gland swelling, Secondary Sjogren's syndrome; **Gastrointestinal complications** - Mesenteric vasculitis leading to intestinal infarction; **Pulmonary Manifestations** (50%) - Pleural effusions, Interstitial lung disease, Parenchymal pulmonary nodules, Diffuse interstitial pulmonary fibrosis; **Cardiac manifestations** - Thickening of the artery walls (atherosclerosis), Arterial stiffness, Risk for myocardial infarction, Myocarditis (with presence of rheumatoid nodules) and myocardial fibrosis(leading to conduction abnormalities).Endocarditis with formation of rheumatoid nodules in the aortic or mitral valves can lead to valvular dysfunction; **Renal manifestations** -Mesangial glomerulo-nephritis, Amyloidosis, Glomerulonephritis, Interstitial renal disease; **Neurological manifestations** - Peripheral neuropathy (diffuse sensorimotor neuropathy or mononeuritis multiplex), Cervical myelopathy, due to atlantoaxial subluxation or pannus formation; **Haematologic manifestations** - Anaemia, Neutropenia, Thrombocytopenia, Thrombocytosis, Eosinophilia, Haematological malignancies.<sup>[27]</sup>

## MANAGEMENT

The primary goal of treating the patient with RA is to maximize long-term health-related quality of life which can be achieved through reduction of inflammation.<sup>[28]</sup> The non-

pharmacotherapy in RA include aerobic activities, dynamic muscular reinforcement and patient education.<sup>[29]</sup>

### **1. Symptomatic management**

Pharmacotherapy include Symptom-modifying antirheumatic drugs (SMARDs) - analgesics (opioid and nonopioid analgesics) to reduce pain, and nonsteroidal anti-inflammatory drugs (NSAIDs) including traditional or nonselective NSAIDs as well as cyclooxygenase-2 [COX-2] inhibitors to lessen pain and stiffness. Both groups of drugs are widely used to control symptoms of RA. Although support for the use of NSAIDs for control of RA symptoms is strong.<sup>[30]</sup> NSAIDs have lost their historical role as a first-line treatment because of concerns about their limited effectiveness, inability to modify the long-term course of the disease and toxic gastrointestinal and cardiac effects.<sup>[31,32]</sup>

### **2. Disease modifying drugs**

Disease-modifying antirheumatic drugs (DMARDs) are a heterogeneous collection of agents grouped together by use and convention. Historically they have been the mainstay of treatment for RA. Methotrexate (MTX) is the dominant DMARD. Sulphasalazine (SSZ) and leflunomide are also widely used DMARDs. Several combinations of DMARDs have proven efficacy.<sup>[33]</sup> An example is MTX, SSZ and hydroxychloroquine – termed triple therapy, or SSZ, MTX and prednisolone, occasionally referred to as COBRA therapy (for Combination therapy Bij Rheumatoid Arthritis).<sup>[34]</sup> They reduce joint swelling and pain, decrease acute-phase markers, limit progressive joint damage and improve function. Patients with RA are at an increased risk for cardiovascular disease. In order to lower this risk, statins are used in clinical practice in addition to biologics.<sup>[35]</sup> Generally, in the treatment of arthritis, a conservative, non surgical treatment is initially adopted.

### **3. Surgical treatment**

When the initial treatment is ineffective, a surgical treatment is then applied. The initial treatment includes drug therapy and injection therapy. In drug therapy, steroidal and non-steroidal anti-inflammatory agents are used. Although the pain-relieving effect of the steroidal agents is prompt and obvious, they may cause many side effects, such as osteoporosis, uncatrized wounds, upper gastrointestinal bleeding and may aggravate existing conditions, such as hypertension, diabetes, etc. Thus, steroidal agents are currently used only in certain limited condition. As for non-steroidal agents, although they also have

good pain-relieving activity, if used for a long-term period, side effects like peptic ulcer, lower limb hydrops, impairment of kidney function, etc., may arise.

Hence, non-steroidal agents are restricted in practical application and have limitations. Therefore, there is still a need in the market for a medicament or method that can efficiently improve the anti-inflammation activity. Recently statin group of drugs is emerging as adjuvants with DMARDs. In a study the composition prepared by mixing a 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor may improve the anti-inflammation effect of hyaluronic acid.<sup>[36]</sup> Another study demonstrates a significant negative association between persistence with statin therapy and RA onset, particularly in adult patients who began treatment at a relatively young age and with high efficacy statins.<sup>[37]</sup>

## STATINS

Statins introduced as hypolipidemic drugs are HMG-CoA reductase inhibitors, mediate clinically significant vascular risk reduction in patients with coronary artery disease by promoting reduction in plasma levels of low-density lipoprotein (LDL) cholesterol. Pravastatin, Simvastatin, Fluvastatin, Atorvastatin, Rosuvastatin, Lovastatin and Pitavastatin are the drugs available in the market.<sup>[38]</sup> Numerous primary and secondary prevention trials confirm clinical benefits with this class of agents.<sup>[39,40]</sup> Some of them may be independent of their cholesterol lowering effects. These so called pleiotropic effects are believed to include anti-inflammatory actions, property to reverse endothelial dysfunction by prevention of LDL oxidation and increasing nitric oxide bioavailability. The anti-oxidant action and ability to provide plaque stability, favourable coagulation profile, prevention of platelet aggregation and to normalize sympathetic out flow as well as anti-proliferative and immunosuppressive properties suggest a new face of statin therapy which make them important not only in the treatment of dyslipidemias and associated complications but also in chronic systemic inflammatory disease states.

Recently, the anti-inflammatory effects of statins have been investigated in humans with diseases characterized by high levels of inflammation such as organ transplantation,<sup>[41,42,43]</sup> multiple sclerosis,<sup>[44]</sup> sepsis<sup>[45]</sup> and RA<sup>[37,46]</sup> indicating beneficial effects. Statins, introduced to the market as lipid-lowering agents, have been shown to reduce cardiovascular morbidity and mortality.<sup>[47,48,49,50,51]</sup> However, there is growing evidence that the beneficial effect of statins cannot be merely explained by their beneficial effect on lipids.<sup>[50,52]</sup> One of the other possible mechanisms is anti-inflammatory.<sup>[53,54,55,56,57]</sup>

This possible anti-inflammatory action has stimulated interest in whether statins might be beneficial in routine disease management of RA. Many trials have been going on with Atorvastatin, Pravastatin, Rosuvastatin and Pitavastatin with RA.<sup>[46,58,59]</sup> As statins have a good safety profile, if beneficial they could routinely be given to RA patients to control disease inflammation. This has the potential to reduce the need for the relatively toxic long-term treatments currently used for RA, such as several disease-modifying anti rheumatic drugs (DMARDs).<sup>[60]</sup>

### STATINS AND IMMUNE SYSTEM

Statins display immune modulatory effects by triggering the major histocompatibility complex (MHC), the co-stimulatory molecules, the leukocyte migration and the cytokine network. Statins interfere with the interaction between MHC (class I/class II) and CD8/CD4 required to achieve efficient T-cell activation. Statins are able to block interferon- $\gamma$  (IFN- $\gamma$ )-induced MHC-II expression on endothelial cells, macrophages and microglia by a mechanism involving block of the IFN- $\gamma$  inducible expression of MHC-II transactivator (CIITA) promoter pIV that regulates the MHC-II expression. Another IFN- $\gamma$  inducible CIITA promoter, promoter I, has also been found to be inhibited by statins.<sup>[55,61,62,63]</sup> Thus, besides the direct immunosuppressive action, the reduced MHC-II availability might be related to potential therapeutic strategies to promote immune tolerance and decrease the rejection of transplanted organs. Nonetheless it might find applications in disorders related to aberrant expression of MHC-II (type I diabetes, multiple sclerosis, rheumatoid arthritis) and chronic inflammatory pathologic conditions.<sup>[64]</sup>

Another component of the immunological synapse selectively blocked by the statin is the lymphocyte function-associated antigen-1 (LFA-1),<sup>[65]</sup> a  $\alpha/\beta$  heterodimeric receptor belonging to the  $\beta 2$  integrin subfamily that plays a central role in lymphocyte homing and leukocyte trafficking.<sup>[66]</sup> The interaction between activated LFA-1 and the intracellular adhesion molecule-1 (ICAM-1) providing signals for both leukocyte migration and co-stimulation is also blocked by statin. Other adhesion molecules in monocytes and T cells have been shown to be inhibited by statins like ICAM-1, CD11b, CD18, and CD49.<sup>[65]</sup> Statins suppress the cytokine-induced maturation of dendritic cells, which consequently fail to express these costimulatory molecules and to induce T-cell response.<sup>[67]</sup> Numerous studies suggest inhibitory effects of statins on proinflammatory cytokine production, such as IFN- $\gamma$ , tumour necrosis factor- $\alpha$ , interleukin (IL)-1 $\beta$ , and IL-6 in several cells, including microglia,

astrocytes, and mononuclear cells. These studies also propose a switch from Th1 to Th2 response by statins. However, whether this switch really occurs remains controversial, because several *in vitro* and *in vivo* models suggest a statin induction of Th2 cytokines, IL-4, IL-5, IL-10 and transforming growth factor (TGF- $\beta$ ),<sup>[62,68]</sup> whereas, in a murine model of inflammatory arthritis, simvastatin suppresses the Th1 response without enhancement of the Th2 response.<sup>[59]</sup>

Other inflammatory mediators reduced by statins are matrix metalloproteinases<sup>[69]</sup> and nitric oxide in microglia and monocytes.<sup>[70]</sup> Another mechanism of immunomodulation is the regulation of isoprenylated proteins such as Rho and Rac and their function.<sup>[71]</sup> The induction of the angiogenic response is a protective physiological mechanism against ischemia and hence is considered a therapeutic strategy for coronary artery and peripheral vascular diseases. On the other hand, pathological angiogenesis is involved in the pathogenesis of cancer, atherosclerosis, diabetic retinopathy, RA and other diseases. Statins were able to inhibit tumour-induced angiogenesis in mice and neovascular growth both *in vitro* and *in vivo*, through RhoA-dependent inhibition of vascular endothelial growth factor receptor (VEGFR), Akt, and focal adhesion kinases.<sup>[72,73]</sup>

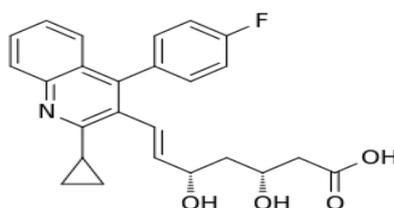
Actually, a dual effect of statins on angiogenesis is reported and explained by a dose-dependent biphasic effect: low doses (between 0.005 and 0.05  $\mu$ M) are proangiogenic and induce the PI3K/Akt pathway, leading to eNOS activation, and high doses are antiangiogenic and induce apoptosis and VEGF down-regulation. All statins significantly ameliorate endothelial dysfunction in patients with coronary artery disease (CAD)<sup>[74]</sup> through low-density lipoprotein cholesterol (LDL-C)-lowering effect and pleiotropic actions such as eNOS up-regulation and nitric oxide (NO) production; through Akt activation; through inhibition of Rho prenylation, antioxidant and anti-inflammatory effects.

## PITAVASTATIN

Pitavastatin, previously known as Itavastatin, Itabavastin, Nisvastatin, NK-104 or NKS-104 the seventh statin is a new member of the statin family. Introduced first in Japan in 2003 to treat primary hyperlipidemia or mixed dyslipidemia and has been licensed for use worldwide, including the USA, Japan, China, Germany, Spain, UK, Australia, France and in INDIA. Pitavastatin was approved for use by the FDA on 08/03/2009. It is a lipophilic statin. The structure of pitavastatin is unique that contributes to a number of pharmacological benefits, including increased systemic bioavailability,<sup>[75]</sup> a high level of oral absorption<sup>[76]</sup> and potent

effects on LDL-C and HDL-C.<sup>[77,78,79]</sup> The high bioavailability of pitavastatin compared to other statins because of its extensive first pass metabolism. Being a lipophilic statin it can easily penetrate hepatic and extra hepatic tissues like bone and exert anti-inflammatory effect.<sup>[80]</sup>

## CHEMISTRY AND SOURCE

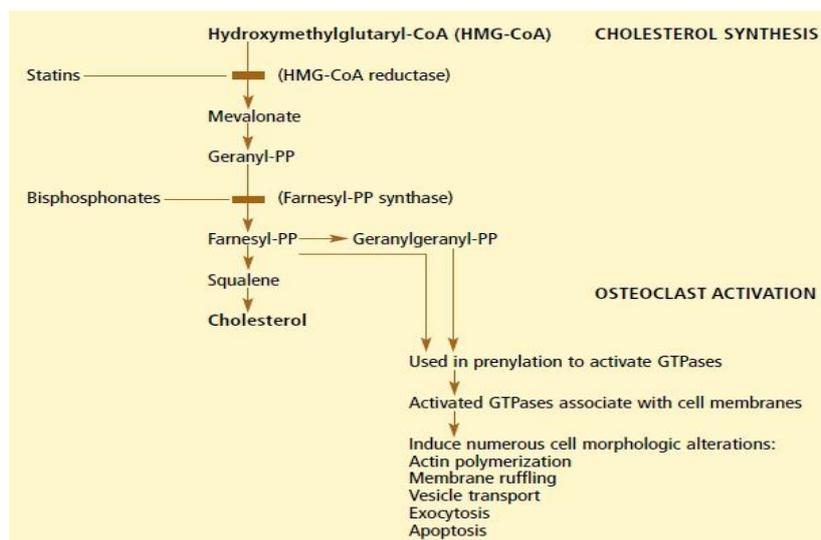


**Structure of Pitavastatin**

The chemical structure of the statins is constituted by two components, the pharmacophore, which is a dihydroxyheptanoic acid segment and its moiety composed of a ring system with different substituents. The function of the pharmacophore relies on the inhibition of the HMG-CoA reductase enzyme in a competitive, dose-dependent and reversible manner. The stereoselectivity of the HMG-CoA reductase enzyme dictates the stereochemistry of the statins, which present two chiral carbon atoms, C3 and C5, on their pharmacophore. The moiety of the pharmacophore, according to the chemical modified ring systems and the nature of the substituents, generates the different structures of the statins. The ring system is a complex hydrophobic structure, covalently linked to the pharmacophore, which is involved in the binding interactions to the HMG-CoA reductase. The structure of the ring is a quinoline in pitavastatin.<sup>[81]</sup> Pitavastatin is a synthetic compound that contains heptanoic acid side chain available as calcium salt.<sup>[82]</sup>

## MECHANISM OF ACTION

The binding interactions of the ring are able to reduce the competition for the binding site between pitavastatin and the endogenous HMG-CoA substrate because keeping the statin closed to the enzyme precludes the possibility of statin displacement by the endogenous substrate.<sup>[81]</sup> HMG Co-A reductors are essential for the synthesis of Cholesterol and this step is the rate limiting step in Cholesterol synthesis. Pitavastatin forms a structural analogue of HMG-CoA intermediate and reversibly compete with the inhibitors of HMG Co-A.<sup>[82]</sup>



## PHARMACOKINETICS

Pitavastatin administered in the  $\beta$  – hydroxy acid form get metabolized in the liver.<sup>[82]</sup> It enters liver by passive diffusion through hepatocytes.<sup>[83]</sup> An efficient first-pass uptake may be more important than high bioavailability to achieve the effect. The bioavailability of pitavastatin is 80% and food intake does not alter its bioavailability.<sup>[84,85]</sup> Half-life of the drug is eleven hours.<sup>[75,85,86]</sup>

Pitavastatin a non-P450-metabolizable statin, is rapidly glucuronized by UGT1A3 and UGT2B7 and then converted to Pitavastatin lactone, its major inactive metabolite, by the glucuronic acid elimination reaction. Unlike other statins, the cyclopropyl group diverts the drug away from metabolism by CYP3A4 and allows only a small amount of CYP2C9-mediated metabolism. Pitavastatin acid, which is the major active form and the inactive lactone form are metabolized to some extent by CYP2C9 and CYP3A4 respectively, in human hepatic microsomes, but the clearance of pitavastatin is very low.<sup>[87]</sup>

## USES

Pitavastatin treatment in long-term smokers was found to reduce LDL-C oxidation and protection of endothelium from oxidative stress. In patients with stable CAD, pitavastatin ameliorate postprandial endothelium-dependent vasodilatation, inhibiting oxidative stress. Pitavastatin is also effective in the treatment of patients with metabolic syndrome or Type2 Diabetes, focusing on its beneficial effects on the atherogenic lipid triad, its neutral effects on glycemic control and its reduced potential for drug to drug Interactions. Pitavastatin is found to have anti epileptogenic effect in Pentylene tetrazol induced seizure in mice.<sup>[88]</sup>

**DOSE, ADMINISTRATION and DURATION**

Available in tablet form in 1, 2 and 4 mg dosage forms.<sup>[82]</sup> Once daily dosage is enough. Generally other statins are usually administered during night time due to peak enzyme activity but pitavastatin can be taken at any time during the day. Almost 80% of the administered dose is absorbed.<sup>[75]</sup>

**SIDE EFFECTS, EFFICACY AND SAFETY**

Common statin-related side effects (headaches, stomach upset, abnormal liver function tests and muscle cramps) are similar to other statins.<sup>[75]</sup> Increased levels of serum uric acid have been reported with pitavastatin.<sup>[89]</sup> Myotoxicity (myalgia, myopathy) occurs in approximately 10% of statin-treated patients and it may progress to rhabdomyolysis, commonly characterized by massive muscle necrosis, myoglobinuria, and acute renal failure. The rank order of myotoxicity was cerivastatin > simvastatin acid > fluvastatin > atorvastatin > lovastatin acid > pitavastatin >> rosuvastatin = pravastatin, without a correlation with their cholesterol-lowering effects.<sup>[90]</sup> The adverse effects are generally due to excessive statin dosing or drug-drug interactions that inhibit statin metabolism.

No data available regarding the occurrence of myopathy and rhabdomyolysis with Pitavastatin. Gemfibrozil reduces clearance of Pitavastatin and raises blood concentrations of the drug.<sup>[82]</sup> The Japanese long-term prospective post-marketing surveillance LIVALO Effectiveness and Safety (LIVES) Study (n = 20,279)<sup>[91]</sup> and the JAPAN-ACS study,<sup>[92]</sup> a prospective, randomized, open-label study in patients with hypercholesterolemia and acute coronary syndrome (ACS) (n = 251) – showed that the LDL-C-lowering efficacy of pitavastatin was similar among patients with and without Type 2 Diabetes (–27.3% vs. –29.7%, respectively, in the LIVES study, and –35.7% vs. 36.4% in the JAPAN-ACS study). The 16-week, randomized head-to-head PATROL trial (n = 302) showed that pitavastatin 2 mg/day has the potency to reduce median LDL-C levels by 41% in patients with risk factors for coronary artery disease and elevated LDL-C levels ( $\geq 3.63$  mmol/l; 140 mg/dl), an effect that was non-inferior to atorvastatin 10 mg/day (44%) and rosuvastatin 2.5 mg/day (42%).<sup>[93]</sup> Furthermore, a subgroup analysis of the 12-week, randomized, open-label CHIBA study (n = 53) showed that the percentage reduction from baseline in LDL-C was significantly greater with pitavastatin than with atorvastatin in patients with Metabolic Syndrome. (45.8% vs. 39.1%; P = 0.0495).<sup>[94]</sup> Pitavastatin is generally well tolerated in hyperlipidemic patients with or without type 2 diabetes, with the most common treatment-related adverse events being

musculoskeletal or gastrointestinal in nature. Increases in plasma creatine kinase levels were seen in <5% of pitavastatin recipients and the incidence of myopathy or rhabdomyolysis was extremely low.<sup>[95]</sup>

Pitavastatin should be carefully administered in patients with liver diseases since plasma concentration of the drug increases in hepatic failure.<sup>[96]</sup> Pitavastatin is contraindicated in pregnancy and lactation.<sup>[75]</sup>

## DRUG INTERACTIONS

Most statins are metabolized by one or more hepatic cytochrome P450 enzymes, leading to an increased potential for drug interactions and problems with certain foods (such as grapefruit juice). Pitavastatin appears to be a substrate of CYP2C9 and not CYP3A4, less likely to interact with drugs that are metabolized via CYP3A4, which might be important for elderly patients who need to take multiple medicine.<sup>[75]</sup> Pitavastatin is contraindicated only in patients treated with cyclosporine or lopinavir/ ritonavir combination therapy. Administration should be temporarily suspended in patients receiving erythromycin or fusidic acid and the dosage should be limited to 2 mg in people treated with rifampicin. In people taking fibrates or niacin pitavastatin should be used with caution.<sup>[97]</sup>

## MONOTHERAPY

1. Trial of Atorvastatin in Rheumatoid Arthritis (TARA), a double blinded randomized placebo control trial among 116 patients with rheumatoid arthritis received 40 mg atorvastatin or placebo as an adjunct to existing disease-modifying antirheumatic drug therapy. Patients were followed up over 6 months and disease activity variables and circulating vascular risk factors were measured. Coprimary outcomes were change in disease activity scores (DAS28) and proportion meeting EULAR (European League against Rheumatism) response criteria. At 6 months, DAS28 improved significantly on atorvastatin (-0.5, 95% CI -0.75 to -0.25) compared with placebo (0.03, -0.23 to 0.28; difference between groups -0.52, 95% CI -0.87 to -0.17,  $p=0.004$ ). DAS28 EULAR response was achieved in 18 of 58 (31%) patients allocated atorvastatin compared with six of 58 (10%) allocated placebo (odds ratio 3.9, 95% CI 1.42-10.72,  $p=0.006$ ). C-reactive protein and erythrocyte sedimentation rate declined by 50% and 28%, respectively, relative to placebo ( $p<0.0001$ ,  $p=0.005$ , respectively). Swollen joint count also fell (-2.69 vs -0.53; mean difference -2.16, 95% CI -3.67 to -0.64,  $p=0.0058$ ). Adverse events occurred with similar frequency in patient's allocated atorvastatin and placebo. Data showed that statins can mediate modest but

clinically apparent anti-inflammatory effects with modification of vascular risk factors in the context of high-grade autoimmune inflammation.<sup>[46]</sup>

2. Some studies highlighted the effect of rosuvastatin on RA patients. Fifty RA patients were randomized in a double-blind placebo-controlled trial to receive either 10 mg of rosuvastatin or placebo as an adjunct to existing disease-modifying antirheumatic therapy. Patients were followed up for a six-month period. Measurements were done at baseline and six months. CRP and IL-6 were measured in the blood. RA disease activity was measured using disease activity score based on 28 joint counts (DAS 28). When analyzing from baseline to six months there was no difference between the rosuvastatin and placebo groups in rheumatoid disease activity (-0.01; standard deviation [SD], 1.08; and +0.18; SD, 0.95; respectively; P value 0.509). There was an improvement in CRP in the rosuvastatin group (-3.23; SD, 18.18) compared with the placebo group (+17.43; SD, 38.03); P value, 0.161. IL-6 showed a trend towards worsening in the rosuvastatin group (+0.15; SD, 1.09) compared with placebo (-0.73; SD, 1.4); P value, 0.054. These data show that rosuvastatin with might decrease the CRP independent to IL-6 in patients with RA but does not improve the overall rheumatoid disease activity.<sup>[98]</sup>

3. A clinical study was performed in Constanta from October 2008 to October 2009, 144 patients were screened (122 women and 22 men) After giving the informed consent, 100 patients were recruited with ages between 18 and 80 years, meeting the 1987 American College of Rheumatology criteria, with active inflammatory disease (defined by disease activity score-DAS28-greater than 2.4) despite ongoing DMARD therapy, in adequate doses for at least 3 months for hydroxychloroquine, or 4 weeks for methotrexate, sulfasalazine, leflunomide, or etanercept. The 100 patients included in the study were divided into two equal groups (one group received simvastatin 20mg/day in addition to prior DMARD therapy and the other, the control group, remained on the same DMARD therapy from the study entry) taking into account the indications of statin therapy. The patients were followed for 6 months, during 3 study visits (at the inclusion, at 3 months, and at 6 months). At each visit visual analogue pain scale, health assessment questionnaire disability index, patient's global assessment of disease activity, physical exam (measuring vital signs and clinical variables of disease activity) and evaluator global assessments of disease activity were found out. Laboratory tests done (hemogram, C-reactive protein, erythrocyte sedimentation rate, transaminases, creatine phosphokinase and only at inclusion and a 6-month visit: lipid profile,

rheumatoid factor, anticyclic citrullinated peptide antibodies, and serum creatinine levels) and disease activity indices like, SDAI, CDAI, and DAS28 (using ESR and CRP) were calculated. During the study and in the statin group, there were 5 dropouts (two in the first 3 months and three in the last 3 months of study) and 95 patients completed the 6-month visit, and in the control group, there were 7 dropouts (one in the first 3 months and six in the last 3 months of study) and 93 completed the 6-month visit Simvastatin at a dose of 20mg/day has small anti-inflammatory effects in patients with rheumatoid arthritis. These effects do not have the magnitude to justify neither the use of statins instead of DMARDs therapy nor their routine use in all patients with rheumatoid arthritis. But thanks to good safety profile, easy administration, and the existence of a broad experience regarding their use in clinical practice, statins are particularly attractive therapeutic agents, so that even a modest efficacy in the treatment of rheumatoid arthritis in association with the reduction of cardiovascular risk can lead to a beneficial therapeutic ratio. This can make statins become particularly useful as adjuvant therapy associated with other conventional therapeutic methods used in rheumatoid arthritis, especially in patients with dyslipidemia, where they should be the first choice of treatment.<sup>[99]</sup>

### COMBINATION THERAPY

1. A placebo control study for eight weeks was conducted at Baghdad with 10 mg of rosuvastatin along with methotrexate. Rosuvastatin reduced very highly significantly CDAI while placebo reduced clinical disease activity index (CDAI) significantly. Also, both rosuvastatin and placebo reduced very highly significantly and health assessment questionnaire disability index (HAQ-DI). However, there was no statistical significant difference between the effect of rosuvastatin and placebo on CDAI and HAQDI. Rosuvastatin has no statistical significant effect on disease activity and functional disability in active RA patients although it was clinically relevant. This may suggest that rosuvastatin can be beneficial and may be used as adjuvant therapy to other medications for treatment of RA.<sup>[100]</sup>

2. Eight weeks double blinded clinical study with 16 highly active RA patients who were on methotrexate, with either atorvastatin 40 mg or rosuvastatin 10 mg as adjuvant therapy show an improvement in clinical parameters like morning stiffness, swollen joint count, visual analogue scale and DAS28 score. ESR also shows improvement. Both the drugs improve the

clinical activity and 10 mg rosuvastatin is equivalent to 40 mg atorvastatin in the management of RA when used as an adjuvant therapy.<sup>[101]</sup>

### CLINICAL OUTCOME OF PITAVASTATIN IN RHEUMATOID ARTHRITIS

Loss of bone mass is frequently seen in patients with RA. The main causes of osteoporosis in patients with RA are seemingly steroid therapy, postmenopausal changes in hormone balance (postmenopausal osteoporosis), and disuse bone atrophy associated with periarticular impairment.<sup>[102;103]</sup> Conversely, bone and cartilage damage in RA results from an imbalance between synthesis and degradation caused by cellular and cytokine-mediated inflammation. Growing evidence demonstrates that the increased bone resorption in bone diseases such as osteoporosis and RA is linked to the facilitation of osteoclast differentiation and activation by inflammatory cytokines of TNF- $\alpha$  and IL-1.<sup>[104,105,106]</sup> Osteoprotegerin (OPG), a secreted soluble decoy receptor with homology to the members of the TNF receptor family, binds to the receptor activator of NF-B ligand (RANKL) and blocks interactions with the receptor activator of NF-B.<sup>[107,109]</sup> An imbalance in this system may play a part in the skeletal complications of RA.<sup>[109]</sup> Statins have recently been reported to stimulate bone formation in vivo<sup>[110,111]</sup> as effectively as vitamin K2 (vit K2), to stimulate osteoblastogenesis, and to inhibit osteoclastogenesis in human bone marrow cell culture<sup>[112]</sup> and also to inhibit bone loss induced by prednisolone (PSL) in rats.<sup>[113]</sup> HMG-CoA reductase inhibitors are also known to increase new bone formation from osteoblasts and to accelerate the promoter activity of bone morphogenic protein-2 (BMP-2), a member of the BMP family.<sup>[110]</sup>

Both bone resorption and bone formation were inhibited by long-term administration of Bisphosphonates (Bis) alone, whereas combination therapy with Bis + statin may be associated with a less marked inhibition of bone metabolism. Cardiovascular disease is highly prevalent in RA patients and some patients are prescribed statins and bisphosphonate. Bis + statin may confer more benefit to the bone metabolism of these patients compared to Bis alone.<sup>[114]</sup> First-line agents for the management of osteoporosis are the aminobiphosphonates. These drugs act to decrease bone resorption by inhibition of the farnesyl diphosphate synthase, which is a step in the Mevalonic acid pathway.<sup>[115]</sup> 3-Hydroxy-3-Methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) inhibit the same pathway at an earlier point and may also antagonize osteoclasts by increasing expression of osteoprotegerin.<sup>[116]</sup>

The more promising applications of pitavastatin on RA are related to its anti-inflammatory effects mediated by both directly through immune modulation and indirectly through

inhibition of platelet functions and ability to modify bone metabolism by stimulating new bone formation.<sup>[80,117]</sup> RA patients are more prone for cardiovascular risks<sup>[118]</sup> and premature atherosclerosis because of chronic inflammation.<sup>[119]</sup> Statins are considered as novel agents in the management of RA based on various animal studies and clinical trials.<sup>[120]</sup> A study comparing cost effectiveness of Pitavastatin versus Atorvastatin showed Pitavastatin is cost effective in managing hypercholesterolemia.<sup>[121]</sup> Another study with Atorvastatin, Pitavastatin, Simvastatin and Rosuvastatin in Spain concluded that among the four statins mentioned, Rosuvastatin is cost effective.<sup>[122]</sup>

## CONCLUSION

Pitavastatin being unique with its metabolism, more potent, minimal side effects compared to other statins available in the market is a boon to use as an adjuvant therapy in patients with RA along with other DMARDs in near future. However more clinical trials are required to confirm the efficacy and safety of pitavastatin in RA.

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