A Systemic Review of Drug Pravastatin Sodium for The Treatment of Atherosclerosis

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ABSTRACT

Background: Pravastatin sodium, one of the 3-hydroxy-3-methylglutaryl-coenzyme A *HMG-CoA reductase* inhibitors (statins) commonly used in the treatment of hypercholesterolemia, possesses pharmacokinetic properties that are unique among statins. Pravastatin sodium is a BCS class iii medication with low permeability and high water solubility (about 300 mg/ml). Due to reduced permeability and high first-pass metabolism, it has a poor absolute oral bioavailability (about 17%). The medication is rapidly absorbed from the upper small intestine, most likely through proton-coupled carrier-mediated transport. As a result, pravastatin sodium (an *HMG-CoA reductase* inhibitor) reduces both the level of low-density lipoprotein cholesterol and the risk of cardiovascular disease in a dose-dependent manner. **Objective:** The primary goal of this study is to describe pravastatin sodium's pharmacology, pharmacokinetic characteristics, clinical safety, and tolerability, as well as its role in the treatment of atherosclerosis. **Method:** A thorough literature search of review articles and research publications from multiple sources was conducted using the terms pravastatin sodium for atherosclerosis, hypercholesterolemia, hypertriglyceridemia, and HMG-CoA reductase inhibitors. PubMed(2000- 2021) scholar on Google (2001-2020) Science Direct (2000-2020) and Web of Science (2000- 2021) are both English-language publications. In addition, drug banks and pub chem, FDA websites are being combed for additional information.

INTRODUCTION:

Hypercholesterolemia is a major factor in the progression of atherosclerotic illnesses in general, and coronary heart disease in particular. At both the individual and social levels, the risk of development of the atherosclerotic process to coronary heart disease increases with increasing levels of total serum cholesterol or low-density lipoprotein (LDL) cholesterol. The diseases of high-income countries are not limited to coronary heart disease. Over the last few decades, the burden of coronary artery disease has disproportionately increased in low- and middle-income nations, which now account for over 80% of all cardiovascular disease deaths. According to the Global Burden of Diseases, Injuries, and Risk Factors Study, coronary artery disease affected an estimated 422 million people and caused an estimated 179 million deaths worldwide in 2015, accounting for 31% of all global deaths; by 2020, the global prevalence of increased coronary artery disease is expected to be 276% or 106670 million people. The prevalence of increasing coronary artery disease grew continuously with age and was higher in males than in women, a percentage change of 5746 percent since 2000. Approximately 236 million people are expected to die each year from coronary heart disease by 2030.

Along with their demonstrated efficacy and safety profile, statins are the treatment of choice for hypercholesterolemia control. They are also playing an increasingly important role in the management of cardiovascular risk in patients with relatively normal plasma cholesterol levels. Although all statins have the same mechanism of action, their chemical structures, pharmacokinetic profiles, and lipid-modifying potency differ. Lipid-lowering medication was unsatisfactory in the 1970s due to its side effects, toxicity, and lack of efficacy. Statins became commercially marketed in the United States in 1987, with lovastatin being the first. Pravastatin was found as a bioactive metabolite of mevastatin in dog urine and was later synthesized by microbial transformation of mevastatin using Streptomyces acidophilus. Pravastatin sodium received FDA approval for the first time in 1991 to treat hypercholesterolemia. Pravastatin, unlike other statins, is relatively hydrophilic and does not appear to be appreciably metabolized by cytochrome P450 enzymes. Because of excellent first-pass uptake, all statins have a selective impact on the liver; lipophilic statins are taken up by passive diffusion through hepatocyte cell membranes, whereas hydrophilic statins are taken up by active diffusion via hepatocyte cell membranes. Pravastatin and rosuvastatin have a higher hepatoselectivity and a lower capacity for peripheral cell absorption than

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lipophilic agents. The clinical pharmacokinetics of pravastatin are reviewed in this article, with an emphasis on the mechanisms that influence particular pharmacokinetic events. The microscopic variables such absorption rate, bioavailability, and clearance. Based on the mechanisms presented, the impact of various conditions (such as diseases and other medicines) on pravastatin pharmacokinetics is also explored. Finally, the importance of mechanistic research in the development of pravastatin's pharmacokinetic-pharmacodynamic correlations is emphasized.

1. CHEMISTRY

1.1. PHYSICOCHEMICAL PROPERTIES:

Pravastatin was first found as a bioactive metabolite of mevastatin in dog urine, and it was later generated via cardia autotrophic microbial transformation of mevastatin utilizing Streptomyces acidophilus (1). Pravastatin is a hygroscopic, crystalline powder with the chemical formula $C_{23}H_{35}NaO_7$ and a molecular weight of 446.52. It is soluble in water and methanol but in chloroform, acetone, and ether it is somewhat insoluble. (2)

It is the only *HMG-CoA reductase* inhibitor with a hydroxyl group at position 6 of the decalin ring among the *HMG-CoA reductase* inhibitors. When compared to lovastatin and simvastatin, this property confers relative hydrophilicity (3). Pravastatin is the only commercially marketed *HMG-CoA reductase* inhibitor that is active in its natural form. It is given as an open acid (- hydroxy acid).formulae of *HMG-CoA reductase* inhibitors are shown in figure 1.
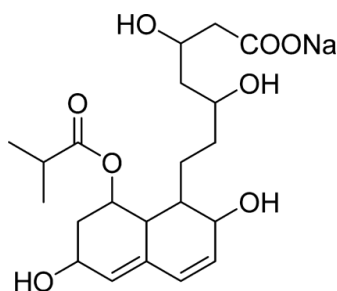

Figure no 1. pravastatin sodium.

As pravastatin is an acid with a pKa of 4.5, its partition coefficient between octanol and water is pH-dependent. (4) The partition coefficient at pH 7 is 0.59, which is 30 000 and 80 000 times lower than those of the lactone forms of lovastatin and simvastatin, respectively.

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1.2. ANALYTICAL METHODS:

In contrast to other statin medicines, which are delivered as inactive lactone prodrugs, pravastatin is supplied in an inactive open active hydroxy acid form. Total reductase inhibitory activity, which is assessed biochemically, is used to determine the total quantity of pravastatin in various tissues and body fluids (5). This approach gives the most precise assessment of the drug's biological effect since it mimics the normal synthesis of mevalonate from HMG-CoA. (6,7) Gas chromatography and mass spectrometry, which may be used to determine the concentration of pravastatin and its metabolites, are the most widely used assays for pravastatin. (8) The assay's highest detection limit for pravastatin is 0.3 g/l.The distribution, metabolism, and elimination (ADME) of pravastatin in the body has also been tracked via radiolabelling investigations, including thin-layer radiochromatography. The method's lowest detection limits for pravastatin are 4.3 g/L for plasma and 0.3 g/L for urine. (9)Bioassay methods can also help to detect total reductase inhibitory activity for the biological effect of pravastatin. (10)

2. PHARMACOKINETIC:

2.1. Absorption and Bioavailability:

Some of the clinical pharmacokinetic properties of pravastatin are summarised in Table I. After oral treatment, pravastatin is rapidly absorbed, with peak plasma concentrations (Cmax) occurring after about 1 hour (range 0.88 to 1.4 hours) (11-16) The average absorption of an oral dose of pravastatin in healthy volunteers is 34%, with a mean absorption time of 2.4 hours, according to radiolabelling studies. The results of the comparison data acquired from both male and female people reveal little variation in the results; The area under the plasma concentration-time curve (AUC) values (90.2 vs 82.5 Ilg/L. h) and Cmax values (38.4 vs 39.8Ilg/L) were also similar (38.4 vs 39.8Ilg/L). (17) Based on AUC and urine excretion of intact pravastatin, the absolute bioavailability after an oral dose average is 18%. When pravastatin is given orally vs intravenously, the poor systemic absolute bioavailability has been linked to both inadequate absorption (34 percent) and hepatic metabolism (first-pass action with subsequent biliary excretion)[18]. Both serum AUC and Cmax values are dose-proportional (figure no.2)[19].

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The decreases in total and LDL cholesterol levels are dose-dependent, however as the dose is increased, the reductions plateau typically, 10, 20, and 40mg of pravastatin given once daily decreases total cholesterol by 16,24 and 25% respectively, and LDL cholesterol by 22, 32, and 34%, respectively. [20] Administration of pravastatin with food decreases the bioavailability of the drug by one-third. Food, on the other hand, raises lovastatin's systemic bioavailability by a third while not affecting fluvastatin or simvastatin. [21] Even though food reduces pravastatin's bioavailability, it does not affect the drug's lipid-lowering action. [22] Pan et al.For example, whether pravastatin 20mg twice a day for 8 weeks was given with meals or 1 hour before meals, LDL cholesterol was reduced to the same extent (36%). Coadministration of the lipid-lowering drug cholestyramine reduces pravastatin absorption, even when the cholestyramine is given 1 hour after the pravastatin.33 individuals with primary hypercholesterolemia were given pravastatin twice a day at doses ranging from 10 to 40 mg/day for four weeks, followed by four weeks of cholestyramine (given with meals and at least one hour after pravastatin).

The addition of cholestyramine decreased pravastatin bioavailability (AVC for pravastatin fell 18 to 49 percent), but increased the lipid-lowering effects (mean total and LDL cholesterol levels decreased 32 and 47 percent, respectively, with the drug combination versus 20 and 27 percent, when pravastatin was given alone). When pravastatin was coupled with cholestyramine for 8 weeks, it resulted in significantly higher reductions in LDL cholesterol (up to 50%), and the combination was more effective than either drug alone. [23] Monotherapy with pravastatin 20mg twice a day or cholestyramine l2g twice daily lowered LDL cholesterol by 31 and 32 percent, respectively, in the same research.

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Table no 01

Population studied	No of patients	Daily dose (mg)	AUC (µg/L*h)	Cmax	tmax	T1/2
Single-dose data						
Healthy men	8	19.2	66.2	27.4	0.88	1.77
Healthy men	16	20	90.2	38.4	1.1	1.3
Patients with hypercholestrolamia	10	20	57	28	1.4	0.8
Steady-state data						
Healthy men	20	40	152.2	64.1	1.05	2.7
Healthy men	8	20	21.8	8.8	1.3	1.5
	8	40	43.7	19	1.1	1.5
	8	80	91.6	40.8	1.3	1.7
Patients with hypercholesterolemia	11	10	21.0	6.1	1.1	2.6
	11	20	30.0	10.5	1.3	3.2
	11	40	75.4	30.6	1.1	2.9

Abbreviations: AUC = area under the plasma concentration-time curve; Cmax = maximal plasma concentration; bid = total daily dose administered in 2 divided doses; GC/NICI-MS = gas chromatography/mass spectrometry with negative-ion chemical ionisation; HPLC = high-performance liquid chromatography; TLRC = thin-layer radiochromatography; tmax = time taken to achieve Cmax; t1,,~ = terminal elimination half-life.

2.2 Distribution:

The volume of distribution (V d) of pravastatin in healthy volunteers is 0.5 L/kg at steady-state [24] and 0.88 L/kg during the elimination phase. In healthy volunteers, protein binding of [14C]pravastatin ranges from 43 to 48 percent, depending on whether the medication is given orally or intravenously. [25]Pravastatin binds to plasma protein at a rate of 55 percent in patients with hypercholesterolemia, compared to 95 and 98 percent for lovastatin and simvastatin, respectively. [26,27]The binding of plasma proteins does not differ considerably between men and women, or between older and younger people. In a clinical trial, there was no evidence of pravastatin in the cerebrospinal fluid after five consecutive doses of 40 mg daily were given.[28]

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2.3 METABOLISM AND EXCRETION:

After significant first-pass metabolism in the liver, the hepatic excretion ratio of pravastatin has been calculated to be 0.66[29]. The active form of pravastatin is transformed into two metabolites, SQ-31-906 (the 3--hydroxy isomeric metabolite) and SQ -31945 (the 3-,5-6-trihydroxy isomeric metabolite), which have 2.5–10 percent of pravastatin's action following the first-pass metabolism in the liver. [30-34] There is no difference in the first converted metabolite between older and younger people. However, conversion of pravastatin into its metabolite after extensive first-pass metabolism is higher in elderly individuals by 15-20% than in younger individuals, indicating that conversion of pravastatin into its metabolite after extensive first-pass metabolism is larger in senior individuals.[35]

Pravastatin's total clearance has been calculated to be 265.9L/h in healthy people [36]and 469.9L/h in those with hypercholesteremia. As a result, we concluded that pravastatin is rapidly excreted from the body. Metabolites are mostly eliminated from an individual's body via renal and non-renal pathways. Both renal and non-renal pathways account for roughly 47 percent and 53 percent of total elimination, respectively. When radiolabeled pravastatin is taken orally, it is shown that 71% of the intact pravastatin is eliminated in the feces and 20% is excreted in the urine. Approximately 80% of pravastatin is excreted after 12 hours of treatment, indicating that pravastatin is rapidly eliminated. [37] Pravastatin's terminal half-life (t1/2) in a healthy person and a patient with hypercholesterolemia is 1.6 hours. Pravastatin does not seem to build in the body after administration of 10, 20, and 40 mg of pravastatin daily, according to a study done over two weeks.[38]

2.4 POTENTIAL FOOD AND DRUG INTERACTIONS:

2.4.1 FOOD INTERACTION:

The rate and degree of medication absorption from the gastrointestinal tract may be affected by food intake. Typically, medication absorption begins in the proximal part of the small intestine, which may be delayed due to the gastrointestinal region's slow emptying. This leads to a decrease in Cmax and an increase in tmax. [39]

When pravastatin was given in solution or capsule form with a high-fat meal, the rate of absorption was reduced, but the extent of absorption was unaffected. As a result, the Cmax was reduced by 50% to 60%, and the tmax was enhanced by 2 to 3 times. In addition, when

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pravastatin was administered with a high-fat meal, its bioavailability was reduced by 30%. The bioavailability of pravastatin was also shown to be reduced by 40% when the medicine was given in the morning and evening, according to a comparative investigation.

2.4.2. DRUG-DRUG INTERACTION:

Drug-drug interactions are especially important in young and elderly people who must take many medications at the same time for some time. Medication is frequently required for a long period in the case of older people. As a result, the review of pravastatin for drug-drug interactions is restricted to a small number of cardiovascular medicines in young and healthy people. The bioavailability of pravastatin is significantly lowered (p0.05) by the injection of cholestyramine, according to a study. [40] It has been observed that the combination improves TC and LDL-c decrease in hypercholesterolemic patients.In healthy people, coadministration of aspirin[41], nicotinic acid[42], rambipril[43], fenofibrate[44], and other 210 mg/day[45] did not impact pravastatin bioavailability. The bioavailability of pravastatin tends to increase when cyclosporine is taken with it in healthy people.

The AUC values in hypercholesterolaemic patients who have received heart transplantation tend to increase significantly. [46] Pravastatin is not metabolized by cytochrome P450 3A4, according to the in vitro and in vivo research. As a result, the steady-state levels of diltiazem, a mild inhibitor of cytochrome P450 3A4, had no effect on the pharmacokinetics of pravastatin during combination therapy. Coadministration of pravastatin with itraconazole, a strong inhibitor of cytochrome 450 3A4, resulted in a slight but statistically significant rise in pravastatin AUC and Cmax. [47]

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3. PHARMACODYNAMIC PROPERTIES:

Table I. Overview of pravastatin pharmacodynamic properties:

1. mechanism of action	Inhibits HMG-CoA reductase, thereby reducing de novo cholesterol biosynthesis and increasing LDL-C receptor expression
Effects on lipids and lipoproteins	Reduces LDL-C and TC, with modest effects on TG and HDL-C. Pravastatin 10 or 20 mg/day significantly reduced Apo B levels during short and long-term studies
Antiatherogenic effects	Prevents the progression of established atherosclerosis and reduces cholesterol deposition in Watanabe heritable hyperlipidaemic rabbits Inhibits oxidized LDL-macrophage growth and prevents the proliferation of foam cells in atherosclerotic lesions invitro. Reduces the number of macrophages in atherosclerotic lesions, and the number of calcified sites and neovascularisation in carotid artery intimal lesions in primates pre-fed an atherogenic diet Reduces arterial intima-media thickness in patients with hypercholesterolemia. Upregulates endothelial nitric oxide synthase in vitro Improves endothelial function in young and middle-aged adults with hypercholesterolemia; although effects in the elderly are less clear Reduces the activity of tumor necrosis factor-α in patients with hypercholesterolemia.
	Reduces platelet thrombus formation in patients with or without CHD, although
Effects on non-lipid risk factors	the decrease is larger in the latter group. Effects on fibrinogen are unclear, with some but not all trials reporting significant reductions Reduces C-reactive protein levels in patients with hypercholesterolemia with and without CHD Improves hyperinsulinemia in elderly patients with hypercholesterolemia.
Apo = apolipoprotein; CHD = coronary heart disease; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol; TG = triglycerides.	

The pharmacodynamic properties of pravastatin are shown in the above table. A brief outline of the pharmacodynamic properties of pravastatin is being given here. There is limited data is available on the elderly group of patients because much pharmacodynamic study is being conducted in healthy individuals of age group 18-39 years. Hence here both the

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pharmacodynamic data of individuals with hypercholesterolemia and individuals with normal cholesterol level is being covered in this section.

3.1. LIPID-LOWERING EFFECTS.

3.1.1 CHOLESTEROL SYNTHESIS AND HMG-COA REDUCTASE ACTIVITY:

Pravastatin is a competitive reversible inhibitor of the microsomal enzyme HMG-COA reductase, which is a major rate-controlling enzyme in the cholesterol production pathways that acts first or early. The conversion of HMG COA to mevalonic acid is prevented when this HMG- COA reductase activity is inhibited [48]. A precursor for the synthesis of sterols, including cholesterol, leads to a reduction in intracellular cholesterol biosynthesis and an increase in microsomal HMG CoA reductase production. and a rise in cell surface low-density lipoprotein expression (LDL) which are primarily found in hepatocyte membranes and are in charge of eliminating LDL cholesterol (LDL-C) from the bloodstream[49,50].

By lowering serum cholesterol levels, receptor-mediated degradation, and clearance of circulating LDL-C occur. [51] Pravastatin also decreased the activity of the cholesteryl ester transfer protein, a plasma glycoprotein responsible for the reverse cholesterol transport pathways of high-density lipoprotein (HDL-C) esters to very-low-density lipoprotein (VLDL) and LDL.[52] The liver is the site of most cholesterol biosynthesis, lipoprotein formation, and LDL catabolism, however, there is some cholesterol biosynthesis in extrahepatic organs. [53] Pravastatin appears to limit cholesterol manufacture in hepatic vs non-hepatic tissues in a selective manner. [54] The liver was shown to be responsible for 90% of cholesterol synthesis, while the testes and spleen had virtually undetectable inhibition (5%). Other statins, such as lovastatin and simvastatin, considerably reduce cholesterol synthesis in all three tissues (>50%)[55].

3.1.2 Lipids and lipoproteins:

Pravastatin has a well-established lipid-lowering impact in younger people. It has also been shown to reduce lipid levels in the elderly. Pravastatin 10 and 20 mg/day reduced total cholesterol and LDL-c by 19-22 percent from baseline in older adults with hypercholesterolemia during a short-term trial period. These levels were found to decrease by 22 percent to 28 percent during a long-term testing period.[56-58]

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3.1.3 Apolipoproteins:

The effect of pravastatin on apolipoprotein, which is essential to control cellular and receptor interaction, demonstrates that a daily dose of 10-20 mg consistently lowers lipoprotein levels by 12-33 percent from baseline in both short and long term studies (four to twelve months)[59-64].

3.2 Antiatherogenic effect:

Pravastatin medication has been found to lower the risk of coronary events. Pravastatin has been shown to have antiatherogenic effects in in vitro and animal studies[65,66,67,68].

The effect of pravastatin on artery intima-media thicknesses (IMT) in patients with hypercholesterolemia has been studied in several studies, as IMT values (especially carotid IMT) are surrogate markers of early atherosclerosis.When compared to placebo, pravastatin 40 mg/day reduced mean carotid, femoral, and combined IMT by 0.06mm (p 0.05), 0.06mm (p 0.05), and 0.05mm (p 0.01), respectively, with no net changes in lumen diameter. Patients having a history of myocardial infarction (MI) had significantly lower common carotid IMT than those whohadnothadaMI.(p<0.05)[33]PravastatinhadastrongereffectonIMTsbetween1.0 and 1.3 mm in size than on those between 1.32 and 1.32 mm (p 0.0001). IMT progression did not correlate with the level of LDL-C decrease in the Carotid Atherosclerosis Italian Ultrasound Study, suggesting that pravastatin may have a direct influence on atherosclerotic growth. [69,70,71,]

4. Clinical Significance Of Pravastatin:

when the patient's renal and hepatic functions are normal Pravastatin is prescribed at a starting dose of 10 mg per day. Depending on the clinical response, the daily dose of pravastatin might be increased to 40mg. When should you take pravastatin? At a daily dose of 1O mg, it reduces total cholesterol, LDL cholesterol, and plasma triglyceride levels by 16, 22, and 15%, respectively, while increasing high-density lipoprotein (HDL) cholesterol levels by 7%. Because cholesterol synthesis is highest at night, pravastatin is taken once daily at bedtime. [72]There has been no evidence of a difference in efficacy dependent on whether the medicine is administered once or twice daily. Pravastatin can be taken with or without food, which is helpful for long-term compliance in a therapy that may be necessary for the rest of one's life. Furthermore, neither gender nor age appears to demand dosage

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changes. Because pravastatin is excreted via two major channels, the kidney, and the liver, it can be given to individuals who have a modest malfunction in one of these organs with very slight dosage modifications. In patients with hepatic illness, however, pravastatin will almost certainly need to be reduced in dose.

Pravastatin's tolerance is enhanced by its apparent inability to pass the lipophilic blood-brain barrier, which may reduce the likelihood of central nervous system side effects such as sleep disturbances[73,74] and headache. Pravastatin, on the other hand, has a low intracellular penetration in peripheral tissues. It's also quickly absorbed and eliminated, and it doesn't build up in plasma after repeated dosing. Its low interaction with most other pharmaceuticals makes it a good choice for people with several medical issues who are taking multiple medications at the same time. However, when any HMG-CoA reductase inhibitor, including pravastatin, is taken with nicotinic acid, gemfibrozil, or cyclosporin, there is an increased risk of myopathy. There isn't enough clinical evidence to say whether pravastatin's hydrophilicity lessens the risk of myopathy. Because pravastatin's protein binding is about half that of other HMG-CoA reductase inhibitors, it should cause little displacement of highly protein-bound medicines.

Pravastatin, for example, has little or no effect on warfarin's clinical anticoagulant action. HMG- CoA reductase inhibitors have become one of the first-line medications for the treatment of hypercholesterolemia due to their efficacy, safety, and ease of administration. Pravastatin is a beneficial member of this class of medicines because of its pharmacokinetic features. Although not as extensive as for bile-acid sequestrants or nicotinic acid, current pharmacokinetic and pharmacodynamic data continue to indicate the significant function of HMGCoA reductase inhibitors in the pharmacological therapy of hypercholesterolemia.

5. Tolerability Of Pravastatin:

Short-term (up to 6 months) and long-term (up to 6 years) treatment of pravastatin 5–40 mg/day was generally well tolerated in the elderly. The incidence of the most commonly occurring adverse events was similar in the pravastatin and placebo groups in short-term, placebo-controlled lipid-lowering trials: musculoskeletal pain (3.3–13.8 percent vs 0–12.5 percent), abdominal pain (3 percent vs 0 percent), headaches (3.3–7.4 percent vs 3.3–10.4 percent), and dizziness (0–9.6 percent vs 3.3–4.3 percent). Diarrhea, fatigue/lethargy, and abnormal liver function tests were among the other 5 percent of pravastatin users who

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experienced side effects. Elevated creatine phosphokinase levels (1 of 30 patients)[75,76] abnormal liver function tests (1 of 30 patients), and severe indigestion (3 of 30 patients) were all thought to be related to pravastatin therapy, though the latter was thought to be due to cholestyramine being taken as part of combination therapy. [77]

In the three long-term, multicenter clinical outcomes studies (PROSPER, LIPID, and CARE), pravastatin and placebo groups experienced equal rates of side events. The most prevalent adverse events in pravastatin and placebo participants in the LIPID study were gastrointestinal events (23% vs 25%), renal or genital system events (18% vs 16%), respiratory disorders (16% vs 16%), and muscular system disorders (16% vs 16%). (13 percent vs 14 percent). The PROSPER and CARE investigations did not identify the kind of frequency of individual adverse events, while the PROSPER trial reported that more than half of all participants (placebo and pravastatin) experienced at least one adverse event throughout the three-year study. Both the PROSPER and LIPID trials found a numerically higher incidence of new cancers in the pravastatin groups (9 percent and 21 percent, respectively) compared to the placebo groups (7 percent and 18 percent, respectively). The between-group difference was significant in the PROSPER trial but not in the LIPID trial.GGI malignancies were shown to be more prevalent in the pravastatin-treated group (65 vs 45 in the placebo group [PROSPER trial]);[78,79,80] However, a meta-analysis of cancer rates from previous randomized, placebo-controlled studies lasting more than 3 years found no link between pravastatin use (or all of them taken together) and an increased risk of cancer (p 0.2).

6. CONCLUSION:

Pravastatin is a highly effective and well-tolerated therapy for hypercholesterolemia, both alone and in combination. Pravastatin (20 mg twice daily) has excellent efficacy. Cholestyramine at 12 g twice daily resulted in very identical decreases in LDL-C values of 31% to 32%. During a clinical trial When the two medications were used together, the LDL-C level reduction was 51%, which was around 60% more than either drug alone. Pravastatin caused small TG reductions and HDL-C increases that were not dosed dependent, whereas cholestyramine increased both TG and HDL-C levels. With combination therapy, the TG effects were canceled, and the gains in HDL-C levels were not additive. Depending on the degree of hypercholesterolemia, treatment may require a mix of medications, similar to how high blood pressure is treated. The lack of a creatine kinase increase with pravastatin and

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similar small increases in aminotransferase levels with cholestyramine and pravastatin at high doses highlight the promise of safety in the use of pravastatin that warrants further investigation, especially in conditions where creatine kinase levels are more likely to rise. The current research shows that pravastatin is a safe and effective treatment for severe hypercholesterolemia. Pravastatin is also well-tolerated in various age groups when given in combination or alone. Individuals' TG and HDL-C levels are also influenced by their TG and HDL-C levels.

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