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# Familial Hypercholesterolemia with an update on role of Mipomersen in its management

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**ABSTRACT**

Familial Hypercholesterolemia (FH) is one of the most common monogenic disorders of lipoprotein metabolism. It is a autosomal dominant disease caused mainly due to mutations in the LDL receptor (LDLR) gene that lead to the plasma accumulation of cholesterol ester-laden LDL (low density lipoprotein) particles. The LDL receptor is a cell surface trans-membrane protein that mediates the uptake & lysosomal degradation of plasma LDL, thereby providing cholesterol to cells. Individuals suffering from FH have elevated plasma levels of LDL, which causes premature coronary atherosclerosis. Mipomersen is an antisense apoB synthesis inhibitor that is currently in development for FH as a new treatment to lower apoB and LDL-cholesterol in patients at high risk of atherosclerotic CHD. Mipomersen is distributed mainly to the liver where it silences apoB mRNA, thereby reducing hepatic apoB-100 and giving rise to reductions in plasma total cholesterol, LDL-cholesterol, and apoB concentrations. Mipomersen has been shown to decrease apoB, LDL-cholesterol and Lipoprotein (a) in patients with heterozygous and homozygous FH on maximally tolerated lipid-lowering therapy. Furthermore, mipomersen has the potential to reduce the frequency of LDL apheresis. mipomersen given alone or in combination with standard lipid lowering medications shows promise as an adjunct therapy in patients with homozygous or refractory heterozygous FH at high risk of atherosclerotic CHD, who are not at target or are intolerant of statins. The long-term efficacy and safety and cost-effectiveness of mipomersen need to be demonstrated.

## INTRODUCTION

FH is one of the most common monogenic disorders of lipoprotein metabolism. It is a autosomal dominant disease caused mainly due to mutations in the LDL receptor (LDLR) gene that lead to the plasma accumulation of cholesterol ester-laden LDL particles.[1]

The LDL receptor is a cell surface trans-membrane protein that mediates the uptake & lysosomal degradation of plasma LDL, thereby providing cholesterol to cells. Individuals suffering from FH have elevated plasma levels of LDL, which causes premature coronary atherosclerosis.[2]

The term FH is used to refer to defects in the genes for Apo lipoprotein (Apo) B, proprotein convertase subtilisin/kexin type 9 (PCSK9).

**Epidemiology**: FH has an estimated worldwide prevalence of 0.2%. Familial hypercholesterolemia in its heterozygous form occurs in around 1 in 500 people in Europe and North America, making it the most common potentially lethal genetic disorder. In some subpopulations there is an increased frequency of FH.

In India, the prevalence of CHD is increasing. Moreover, the disease is seen in the younger population. Since Familial Hypercholesterolemia (FH)

is one of its major correctable causes, timely treatment of FH can control the prevalence of CHD.[2]

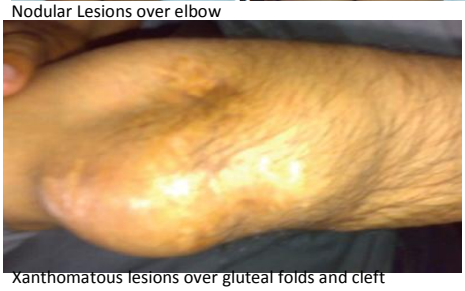
**Pathology:** Currently, known causes of FH include mutations in the LDL receptor (LDLR), Apo B (APOB), or proprotein convertase subtilisin/ kexin type 9 (PCSK9) genes. There are over 1600 known mutations of the LDLR gene documented to cause FH accounting for about 85 to 90% of FH cases.[3]

FH occurs clinically in two forms: heterozygous and homozygous. FH heterozygotes inherit one mutant LDL receptor allele, manifest a two-to-three fold elevation in plasma LDL-cholesterol and typically develop premature coronary heart disease after age 35. FH homozygotes inherit two mutant LDL receptor alleles, are rare, have six to eight fold elevation in plasma concentrations of LDL-cholesterol and often die of myocardial infarctions during the first two decades of life. It is also seen that some phenotypic FH homozygotes inherit two identical mutant LDL receptor alleles (true homozygotes) while some inherit two different mutant alleles (compound heterozygotes).[3]

Individuals suffering from FH have elevated plasma levels of LDL, which causes premature atherosclerosis.

The characteristic clinical syndrome in adulthood comprises an increased serum cholesterol concentration, tendon xanthomas, and premature coronary heart disease,

Nodular Lesions over elbow



Xanthomatous lesions over gluteal folds and cleft

Total cholesterol concentrations in heterozygous FH patients (genetic defect inherited from one parent) are typically in the range of 350 to 550 mg/dL and in homozygotes (genetic defects inherited from both parents) range from 650 to 1000 mg/dL

Because FH is due to a genetic defect or defects, hypercholesterolemia is present from childhood, leading to early development of CHD. Of particular concern are FH homozygotes, in which the severity of hypercholesterolemia usually results in severe atherosclerosis and even cardiovascular disease during childhood and adolescence.[3]

**Clinical features** [4,5,6,7]

Signs and symptoms of homozygous FH in children include Symptoms consistent with ischemic heart disease, peripheral vascular disease, cerebrovascular disease, or aortic stenosis; Articular symptoms such as tendonitis or arthralgia's; Unusual skin lesions, such as cutaneous xanthomas at birth or by early childhood (e.g. planar xanthomas, tuberous xanthomas; later, tendon xanthomas) ; Corneal arcus; and Murmur of aortic stenosis. Most patients with homozygous FH do not survive adulthood beyond age 30 years unless treated with unusual methods, such as liver transplantation, LDL apheresis, or ileal bypass surgery to dramatically lower their LDL-C levels.

Children with heterozygous FH do not have symptoms related to CHD, and most do not develop tendon xanthomas or corneal arcus. However, one parent will have severe hypercholesterolemia and will also probably have either a personal or family history for premature CAD.

Signs and symptoms of heterozygous FH in adults include Long-standing history of severe hypercholesterolemia dating back to childhood; if no previous acute coronary event, symptoms consistent with ischemic heart disease, especially in the presence of other cardiovascular risk factors (especially smoking); Past or present symptoms of recurrent Achilles tendonitis or arthritic complaints and Xanthelasmas. If heterozygous FH is left untreated, tendon xanthomas (Achilles tendons, metacarpophalangeal [MCP] extensor tendons) will

occur by third decade of life in more than 60% of patients.

**Diagnosis** [8,9]

The clinical diagnosis of FH is most likely when two or more first-degree relatives are found to have elevated LDL cholesterol in the range noted above, when pediatric cases are identified in the family, or when the patient or a close relative has tendon xanthomas.

Genetic screening is useful when the diagnosis is uncertain.

**Lipid analysis:** Homozygous FH: Severely elevated cholesterol levels (total cholesterol and LDL-C levels >600 mg/dL); triglyceride levels within the reference range

Heterozygous FH: Elevated LDL-C levels commonly greater than 250 mg/dl; in patients younger than 20 years, an LDL-C level higher than 200 mg/dl is highly suggestive of heterozygous FH or, possibly, familial ligand defective apoB-100; in adults, LDL-C levels higher than 290-300 mg/dl suggest heterozygous FH

LDL receptor analysis can be used to identify the specific LDL receptor defect, and LDL receptor or apoB-100 studies can help distinguish heterozygous FH from the similar syndrome of familial defective apoB-100.

**Imaging Studies:** An echocardiogram is indicated for children with homozygous FH, especially those who have a murmur or symptoms suggestive of aortic stenosis or another valve abnormality. Children with homozygous FH should be referred to a pediatric cardiologist for consideration of vascular imaging studies (PET scan, determination of carotid intima medial thickness, coronary catheterization) that can direct treatment for hypercholesterolemia. Radiographic imaging of the Achilles tendon helps accurately measure Achilles tendon xanthomas, but the findings do not change lipid management.

**Tests to rule out secondary hypercholesterolemia:** Other laboratory testing may be suggestive by findings discerned thorough history and physical examination. In the absence of symptoms or signs suggestive of a particular disorder, a limited workup should be performed to rule out secondary hypercholesterolemia. Basic tests to rule out diabetes, hypothyroidism, hepatic disease, and renal disease are usually sufficient.

**Prevention** [10]

Universal screening for elevated serum cholesterol is recommended. FH should be suspected when untreated fasting LDL cholesterol or non- HDL cholesterol levels are at or above the following:

- Adults (>/=20 years): LDL cholesterol >/=190 mg/dL or non-HDL cholesterol >/=220 mg/dL;
- Children, adolescents and young adults (<20 years): LDL cholesterol >/=160 mg/dL or non- HDL cholesterol >/=190 mg/dL.

For all individuals with these levels, a family history of high cholesterol and heart disease in first-degree relatives should be collected. The likelihood of FH is higher in individuals with a positive family history of hypercholesterolemia or of premature CHD (onset in men before age 55 years and women before age 65 years).

Cholesterol screening should be considered beginning at age 2 for children with a family history of premature cardiovascular disease or elevated cholesterol. All individuals should be screened by age 20.

**Management:** The management of FH patients especially homozygotes has been a challenging job. Besides dietary control, a number of therapies have been advocated and early institution of such therapy may increase the long-term survival rates.

HMG COA reductase inhibitors known as statins are remarkably effective in lowering the LDL cholesterol levels. Combination therapy with ezetimibe, selectively blocking cholesterol absorption in the gut results in further modest decline in LDL levels. It has largely replaced the bile acid sequestrants. Other cholesterol lowering medications like nicotinic acid and fibrates have less often been used in children. The NCEP expert panel for children and adolescents recommends that consideration may be given to pharmacologic treatment of hyperlipidemia if the child is at least 10 years of old and the adequate period of

dietary restriction, at least 6 months, has not achieved therapeutic goals.[11]

The goal of FH treatment is to reduce the risk of CHD or risk of a CHD-equivalent condition (e.g. carotid artery disease, diabetes, peripheral arterial disease).

Adult FH treatment recommendations [12]

1. All adult FH patients should receive long-term cholesterol-lowering therapy to reduce LDL-C by >50% Almost all will require a high dose statin

2. Intensification of cholesterol-lowering therapy should be considered in higher risk FH patients like Clinically evident CHD or other cardiovascular disease, Diabetes, Family history of very premature onset CHD (first degree relative male <45 years or female <55 years), Current smoking (strongly encourage smoking cessation), Two or more cardiovascular risk factors other than smoking. Most will require ezetimibe or another drug in combination with a high dose statin. The potential benefit for an individual patient should be weighed against the potential for adverse effects, cost, and decreasing adherence with multidrug regimens.

3. Intensification of therapy may be considered in lower risk FH patients after the initial >50% reduction in LDL-C

4. Treat other cardiovascular risk factors - Emphasize a healthy diet, regular physical activity and weight control, Avoid tobacco, Control blood pressure <140/<90 mm Hg (Diabetes: <130/<80 mm Hg), Low-dose aspirin for those with cardiovascular disease or diabetes

5. Consider referral to a lipid specialist for more aggressive lipid management and Cascade testing to identify relatives with FH

Management of homozygous FH: [3,12]

- Lifestyle changes: Recommended for cardiovascular benefits
- High doses of HMG-CoA reductase inhibitors (statins) combined with bile acid sequestrants, ezetimibe, and niacin
- Estrogen replacement therapy in postmenopausal women
- LDL apheresis for selective removal of lipoproteins that contain apo-B (when the LDL receptors are absent or nonfunctional)
- Surgical procedures: Portacaval anastomosis or Liver transplantation (rarely)

Management of heterozygous FH: [3,12]

- Lifestyle modification, including diet (limited saturated fats, *trans* fats, and cholesterol); weight management; aerobic/toning exercises
- HMG-CoA reductase inhibitors (statins) (eg, simvastatin, atorvastatin, or rosuvastatin), and one or more other LDL lowering medications,
- Bile acid sequestrants,
- Ezetimibe,
- Niacin
- Estrogen replacement therapy in postmenopausal women

Consider LDL apheresis for patients with documented CHD whose LDL-C level cannot be lowered below 200 mg/dL by conventional therapy or Those without CHD but who have an LDL-C level greater than 300 mg/dL

Other potential new treatments are PCSK9 inhibitors; MTTP inhibitors like Lomitapide; CETP inhibitors like Torcetrapib, Dalcetrapib, Anacetrapib; and Mipomersen. [13]

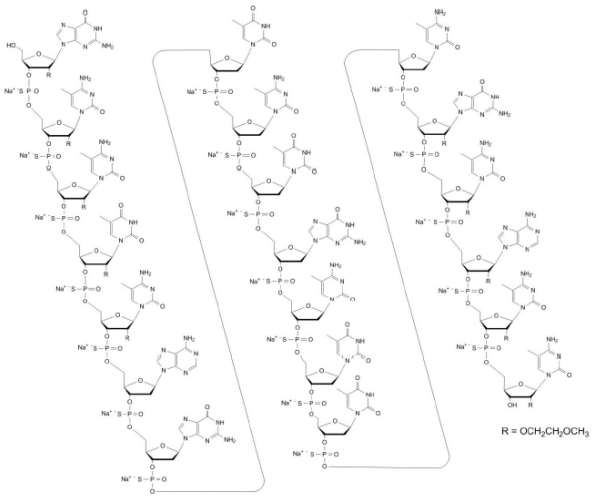
**Mipomersen:** ApoB is the principal apolipoprotein of LDL and its metabolic precursor, very low density lipoprotein (VLDL).

It is an oligonucleotide inhibitor of apolipoprotein B-100 synthesis indicated as an adjunct to lipid-lowering medications and diet to reduce low density lipoprotein-cholesterol (LDL-C), apolipoprotein B (apo B), total cholesterol (TC), and non-high density lipoprotein-cholesterol (non HDL-C) in patients with homozygous familial hypercholesterolemia [14,15]

The recommended dose is 200 milligrams (mg) once weekly as a subcutaneous injection. It is intended for subcutaneous use only. The injection should be given on the same day every week, but if a dose is missed,

the injection should be given at least 3 days from the next weekly dose

Mipomersen sodium is represented by the following structural formula:




The molecular formula of mipomersen sodium is $C_{230}H_{305}N_{67}O_{122}P_{19}S_{19}Na_{19}$ and the

**Pharmacology:** Mipomersen is an antisense oligonucleotide targeted to human messenger ribonucleic acid (mRNA) for Apo B-100, the principal Apo lipoprotein of LDL and its metabolic precursor, VLDL. Mipomersen is complementary to the coding region of the mRNA for Apo B-100, and binds by Watson and Crick base pairing. The hybridization of mipomersen to the cognate mRNA results in RNase H-mediated degradation of the cognate mRNA thus inhibiting translation of the Apo B-100 protein.

At a concentration of 3.8 times the Cmax of the maximum recommended dose (200 mg subcutaneous injection), mipomersen does not prolong the QTc interval to any clinically relevant extent.

The peak concentrations after absorption is seen at 3 to 4 hours. The Bioavailability is 54% to 78% over a dose range of 50 mg to 400 mg. It is highly bound to human plasma proteins (≥ 90%). Distribution plasma half-life is of approximately 2 to 5 hours. It is metabolized in tissues by endonucleases to form shorter oligonucleotides that are then substrates for additional metabolism by exonucleases. The elimination of mipomersen involves both metabolism in tissues and excretion, primarily in urine. Elimination half-life for mipomersen is approximately 1 to 2 months. [14,15]

No clinically relevant pharmacokinetic interactions were reported between mipomersen and warfarin, or between mipomersen and simvastatin or ezetimibe. Pharmacokinetics in patients with renal impairment or hepatic impairment has not been established

However mipomersen is contraindicated in Moderate or severe hepatic impairment (Child-Pugh B or C) or active liver disease, including unexplained persistent elevations of serum transaminases and in Patients with a known hypersensitivity to any component of this product

Hence after initiation of mipomersen therapy lipid levels should be monitored at least every 3 months for the first year. There is concern that mipomersen could induce elevations in transaminases and steatohepatitis, which can progress to cirrhosis over several years. In a clinical trial, 4 (12%) of the 34 subjects with Homozygous FH treated with mipomersen compared to 0% of the 17 subjects treated with placebo had an elevation in ALT ≥ 3x ULN, and 3 (9%) of those treated with mipomersen compared to 0% treated with placebo had at least one elevation in ALT ≥ 5x ULN. [14,15]

It is necessary to Measure a full liver panel to include ALT, AST, total bilirubin, and alkaline phosphatase before initiation of treatment with mipomersen. If the baseline liver-related tests are abnormal, mipomersen may be initiated after an appropriate work-up and the baseline abnormalities are explained or resolved. During the first year, liver-related tests should be conducted monthly. After the first year, these tests should be conducted at least every 3 months. Mipomersen should be Discontinued for persistent or clinically significant elevations. If transaminase elevations are accompanied by clinical symptoms of liver injury (e.g., nausea, vomiting, abdominal pain, fever, jaundice, lethargy, flu-like symptoms), increases in bilirubin ≥2x ULN, or active liver disease, Mipomersen should be Discontinued and the probable cause should be identified. [14,15]

In the pooled, placebo-controlled clinical trials with mipomersen, elevated serum transaminase levels,

mainly ALT, have been observed. Elevated ALT levels ≥ 3X ULN have been reported on two consecutive occasions at least 7 days apart in 8.4% of patients receiving mipomersen therapy (versus 0% of placebo patients) with 16.5% of patients receiving mipomersen therapy having at least 1 result that was ≥ 3X ULN (versus 0.8% for placebo patients). The ALT elevations observed in the pooled, placebo-controlled trials were generally accompanied by lesser AST elevations and were not associated with increased total bilirubin, changes in INR or PTT, nor by decreased albumin levels. After stopping therapy, in the patients in whom an elevation was observed, transaminase elevations trended toward baseline over a period of weeks to months. [14,15]

Increases in liver fat as measured by MRI were greater in patients receiving mipomersen therapy than in patients receiving placebo. Data from Phase 3 supportive trials in patients with heterozygous familial hypercholesterolemia and coronary artery disease and in patients with high risk hypercholesterolemia demonstrated after 26 weeks of treatment, a median nominal increase in fat fraction of 9.6% relative to baseline following mipomersen therapy versus a nominal 0.02% change in the placebo group (mean increases were 12.2% mipomersen vs 0.4% placebo). The maximum change in fat fraction was 46% for the mipomersen group and 28% for the placebo group. Sixty-two percent of patients receiving mipomersen developed a 5% or greater increase in hepatic fat versus 8% of patients receiving placebo. In general, these elevations in fat fraction decreased when assessed by MRI performed 24 weeks after cessation of mipomersen in the Phase 3 trial of patients with high-risk hypercholesterolemia. In the open-label extension trial, among individuals with a measurement at baseline and at 12 months or longer on mipomersen, 25% had an average liver fat fraction > 20% on at least one occasion. [14,15]

During the clinical trials in patients with heterozygous familial hypercholesterolemia (HeFH) and hyperlipidemia, the median absolute increase in hepatic fat was 10% after 26 weeks of treatment, from 0% at baseline, measured by magnetic resonance imaging (MRI). Alcohol may increase levels of hepatic fat and induce or exacerbate liver injury. It is recommended that patients taking mipomersen should consume no more than one alcoholic drink per day. Caution should be exercised when mipomersen is used with other medications known to have potential for hepatotoxicity, for example isotretinoin, amiodarone, acetaminophen (>4 g/day for ≥3 days/week), methotrexate, tetracyclines, and tamoxifen. In such cases, if the drugs are to be used, then more frequent monitoring of liver-related tests may be warranted.

Mipomersen has not been studied concomitantly with other LDL-lowering agents that can also increase hepatic fat. Therefore, the combined use of such agents is not recommended.

Injection site reactions have been reported in 84% of patients receiving mipomersen therapy. These local reactions typically consist of erythema, pain, tenderness, pruritus and local swelling. These reactions have resulted in discontinuation of therapy in 5% of patients in pooled Phase 3 trials. Hence to minimize the potential for injection site reactions, proper technique for subcutaneous administration should be followed. [14,15]

Flu-like symptoms like influenza-like illness, pyrexia, chills, myalgia, arthralgia, malaise or fatigue have been reported in 30% of patients receiving mipomersen therapy resulted in discontinuation of therapy in 3% of patients in pooled Phase 3 trials.

Immunogenicity reactions were noted in mipomersen trials. In the pooled Phase 3 trials, 38% of mipomersen-treated patients tested positive for anti-mipomersen antibodies during the 6-month trials. Efficacy results in the Phase 3 trials in patients who tested positive for anti-mipomersen antibodies were similar to patients who remained negative for antibodies (mean LDL-C percent change from baseline was -32% for antibody-positive and -34% for antibody-negative participants). In the open-label extension trial, approximately 72% of patients receiving mipomersen therapy tested positive for anti-mipomersen antibodies (35% with titers >3200). The incidence of flu-like symptoms and the incidence of discontinuation of mipomersen were higher in antibody-positive patients. Antibodies to mipomersen were associated with higher trough levels for the

drug. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to MIPOMERSEN with the incidence of antibodies to other products may be misleading. [14,15]

It is a Pregnancy Category B and may cause fetal harm. Hence this drug should be used during pregnancy only if clearly needed. Females of reproductive potential should use effective contraception during mipomersen therapy. If Females become pregnant during mipomersen therapy, then they should notify their healthcare provider. It is not known whether mipomersen is excreted in human milk. Because many drugs are excreted in human milk a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother. Safety and effectiveness have not been established in pediatric patients. Clinical studies of mipomersen did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Of the 51 patients enrolled in the Phase 3 trial in HoFH, the mean age was 31 years and the oldest patient in the trial was 53 years. Of the 261 patients who received mipomersen in the pooled Phase 3 trials, 59 (22.6%) were ≥65 years old and 10 (3.8%) were ≥75 years old. In the pooled Phase 3 trials, patients ≥ 65 years of age treated with mipomersen had a higher incidence of hypertension and peripheral edema compared to placebo patients in this age group, as well as compared to the younger mipomersen-treated age group. Hepatic steatosis was also reported with greater frequency in the ≥ 65 group (13.6%) compared to the <65 group (10.4%). The safety and efficacy of mipomersen treatment in patients with known renal impairment or in patients undergoing renal dialysis have not been established. Due to the lack of clinical data and mipomersen's renal safety profile, mipomersen is not recommended in patients with severe renal impairment, clinically significant proteinuria, or on renal dialysis. The safety and efficacy of mipomersen treatment in patients with known hepatic impairment have not been established. Mipomersen is contraindicated in patients with clinically significant hepatic dysfunction, which may include persistent elevations of transaminases. [14]

There have been no reports of overdose with mipomersen treatment. In clinical trials, patients receiving higher doses of mipomersen (300 mg and 400 mg once weekly for 13 weeks) experienced adverse reactions similar to the adverse reactions experienced by patients receiving treatment with 200 mg once weekly but at slightly higher rates and greater severity. Liver-related tests should be monitored. Although there is no information on the effect of hemodialysis in treating an overdose with mipomersen, hemodialysis is unlikely to be useful in overdose management since mipomersen is highly bound to plasma proteins. [14]

**Clinical efficacy:** Phase I trials showed that, in healthy individuals with mild dyslipidemia, mipomersen produces rapid and dose-dependent prolonged reductions in serum apoB, and LDL-cholesterol. ApoB was reduced by a maximum of 50% from baseline. This decrease in apoB coincided with a maximum 35% reduction of LDL-C. LDL-C and apoB remained significantly below baseline ($P<0.05$) up to 3 months after the last dose. [16]

Subsequent Phase II and III trials have demonstrated that mipomersen is an effective lipid-lowering therapy in FH. A Phase II trial in 44 heterozygous FH patients already taking conventional lipid-lowering therapy demonstrated that 300 mg doses of mipomersen could safely, further reduce plasma apoB and LDL-cholesterol concentrations by one-third. Patients were randomized to receive subcutaneous mipomersen (50, 100, 200 or 300 mg) or placebo on days 1, 4, 8 and 11, followed by once-weekly injections to a total of 6 weeks. Mipomersen produced significant reductions in LDL cholesterol and other atherogenic apolipoprotein B-containing lipoproteins. After 6 weeks of treatment, the LDL cholesterol level was reduced by 21% from baseline

in the 200-mg/week dose group (p <0.05) and 34% from baseline in the 300-mg/week dose group (p <0.01), with a concomitant reduction in apolipoprotein B of 23% (p <0.05) and 33% (p <0.01), respectively. [17]

A dose-escalation Phase 2 study showed that Mipomersen showed promise for treatment of patients not reaching target LDL cholesterol levels on stable statin therapy. Seventy-four subjects were enrolled sequentially into 1 of 6 dose cohorts at a 4:1 (active/placebo) ratio. Subjects received 7 doses of 30 to 400 mg over 5 weeks in the first 5 cohorts and 15 doses of 200 mg over 13 weeks in the sixth cohort. end points included percentage change from baseline in apo B and LDL cholesterol. The apo B and LDL cholesterol were reduced by 19% to 54% and 21% to 52%, respectively, at doses of 100 mg/week mipomersen and higher in the 5-week treatment cohorts. Efficacy seemed to increase upon treatment for 13 weeks at a dose of 200 mg/week. [18]

The efficacy and safety 200 mg/week of mipomersen has also been assessed by Visser et al in placebo-controlled study in 21 patients with familial hypercholesterolemia. The patients received a weekly subcutaneous dose of 200 mg mipomersen or placebo for 13 weeks while continuing conventional lipid lowering therapy. Thirteen weeks of mipomersen administration reduced LDL-cholesterol by 22.0 (17.8) % and apoB by 19.9 (17.4) % and there was a trend toward an increase in intra-hepatic triglyceride content (IHTG) content. [19]

The efficacy and safety of 200 mg/week mipomersen has also been assessed in homozygous FH by Raal FJ in a placebo-controlled, phase 3 study which showed that Inhibition of apolipoprotein B synthesis by mipomersen is effective therapy to reduce LDL cholesterol concentrations in patients with homozygous familial hypercholesterolemia who are already receiving lipid-lowering drugs, including high-dose statins. Patients were aged 12 years and older with clinical diagnosis or genetic confirmation of homozygous familial hypercholesterolemia, who were already receiving the maximum tolerated dose of a lipid-lowering drug. The primary endpoint was percentage change in LDL cholesterol concentration from baseline. 34 patients were assigned to mipomersen and 17 to placebo. The mean percentage change in LDL cholesterol concentration was significantly greater with mipomersen (-24.7%, 95% CI -31.6 to -17.7) than with placebo (-3.3%, -12.1 to 5.5; p=0.0003). [20]

Akdim F et al evaluated the efficacy and safety of mipomersen monotherapy with or without dose loading in subjects with mild-to-moderate hyperlipidaemia in a placebo-controlled, dose-escalation study. Fifty subjects with LDL-cholesterol levels between 119 and 266 mg/dL were enrolled into five cohorts at a 4:1 randomization ratio of active to placebo. Two 13-week dose regimens were evaluated at doses ranging from 50 to 400 mg/week. Mipomersen produced dose-dependent reductions in all apoB containing lipoproteins. In the 200 and 300 mg/week dose cohorts, mean reductions from baseline in LDL cholesterol were -45 ± 10% (P= 0.000) and -61 ± 8% (P= 0.000), corresponding to a -46 ± 11% (P= 0.000) and -61 ± 7% (P= 0.000) decrease in apoB levels. Triglyceride levels were also lowered with median reductions up to 53% (P= 0.021). Hence it was shown that Mipomersen administered as monotherapy in subjects with mild-to-moderate hyperlipidaemia produced potent reductions in all apoB-containing lipoproteins. But higher doses were associated with hepatic transaminase increases. [21]

Visser et al examined the effect of mipomersen in 33 statin-intolerant patients at high risk for cardiovascular disease. Over half of the patients were FH heterozygotes. Treatment with 200 mg/week mipomersen for 26 weeks resulted in a 47% decrease in LDL-cholesterol, ranging from −19% to −77%. This was predominantly the result of a reduction in small LDL particles rather than large LDL particles. While triglycerides and Lipoprotein (a) levels were significantly reduced by mipomersen treatment, HDL-cholesterol and apoA-I concentrations did not change. This data suggest that mipomersen is a potential therapeutic option in statin-intolerant patients at high risk for CVD. However The long-term follow-up of liver safety is required. [22]

In a placebo-controlled, phase 3 trial, patients with HeFH and coronary artery disease on maximally tolerated statin and LDL-C ≥2.6 mmol/L (≥100 mg/dL) were randomized to weekly subcutaneous mipomersen 200 mg or placebo (2:1) for 26 weeks. The primary end point was percent change in LDL-C from baseline at week 28. Mean (95% confidence interval) LDL-C decreased significantly with mipomersen (-28.0% [-34.0% to -22.1%] compared with 5.2% [-0.5% to 10.9%] increase with placebo; P<0.001). Mipomersen significantly reduced apolipoprotein B (-26.3%), total cholesterol (-19.4%), and lipoprotein(a) (-21.1%) compared with placebo (all P<0.001). thus it was shown that Mipomersen is an effective therapy to further reduce apolipoprotein B-containing lipoproteins, including LDL and lipoprotein(a), in HeFH patients with coronary artery disease on statins and other lipid-lowering therapy. [23]

In a double-blind, placebo-controlled, multicenter trial. Patients (58) were ≥18 years with LDL-C ≥7.8 mmol/L or LDL-C ≥5.1 mmol/L plus CHD disease, on maximally tolerated lipid-lowering therapy that excluded apheresis. Weekly subcutaneous injections of mipomersen 200 mg (n =39) or placebo (n =19) were added to lipid-lowering therapy for 26 weeks.the endpoint was percent reduction in LDL-C from baseline to 2 weeks after the last dose of treatment.it was seen that Mipomersen (n=27) reduced LDL-C by 36%, from a baseline of 7.2 mmol/L, for a mean absolute reduction of 2.6 mmol/L. Conversely, mean LDL-C increased 13% in placebo (n=18) from a baseline of 6.5 mmol/L (mipomersen vs placebo p<0.001). Mipomersen produced statistically significant (p<0.001) reductions in apolipoprotein B and lipoprotein(a), with no change in high-density lipoprotein cholesterol. [24]

In a trial done on 123 patients with heterozygous FH and coronary artery disease on maximally tolerated lipid-lowering therapy, Mipomersen decreased LDL-C by 28% (baseline 153 mg/dl), Lipoprotein (a) by 21% (baseline 45 mg/dl). Mipomersen reduced the percentage of patients with LDL-C ≥ 4.14 mmol/l from 39 to 2%, with LDL ≥ 3.36 mmol/l from 62 to 16%, with LDL ≥ 2.59 mmol/l from 98 to 54%, and with Lp(a) ≥ 60 mg/dl from 39 to 23%. Thus it was noted that when added to maximally tolerated lipid-lowering therapy, mipomersen may reduce the necessity for apheresis in many of these patients [25]

Safety

The majority of patients treated with mipomersen experience mild, transient injection site reactions, and about one-third experience flu-like symptoms. However, the mipomersen' s safety concerns has been with incidence of hepatic steatosis, as this was the major issue with suppression of VLDL production using Mipomersen. Elevated plasma liver transaminases are common in patients on mipomersen therapy, and may be associated with the development of steatosis. [23,24,25]

The impact of 200 mg/week mipomersen on intrahepatic triglyceride content, assessed by proton magnetic resonance spectroscopy (1H-MRS), was studied in 21 patients with heterozygous FH. Liver fat content was assessed at baseline, where the mean intrahepatic triglyceride content was 1.2%, and again at weeks 4 and 15. The most common adverse events were injection site reactions, which affected all patients in the mipomersen group (19% of injections) compared to 73% of the placebo (9% of injections). Flu-like symptoms were observed in 70% of the mipomersen group and 18% of placebo. No clinically significant increases in ALT were observed. The mean intrahepatic triglyceride content increased 0.8 percentage points in the mipomersen group at week 15, compared to a decrease of 0.1 percentage points in the placebo group (P = 0.051). In one patient, liver fat increased from 0.6% at baseline to 5.7% at week 15, but this appeared to be reversible, decreasing to 2.5% at week 35. [23,24,25]

In a Phase III trial of homozygous FH patients, 1H-MRS quantification of liver fat content was performed at baseline and only remeasured in patients with increases in ALT greater than three times the upper reference limit. This corresponded to four patients (12%) in the mipomersen group, and none in the placebo group. [23,24,25]

In a trial of 33 statin-intolerant patients, the majority with FH, 81% of mipomersen-treated patients had increases in ALT above the upper limit of normal, compared to 25% of the placebo group. One-third of

mipomersen-treated patients showed persistent elevations in liver transaminases greater than three times the upper reference limit. Hepatic steatosis was detected in 12 of 14 patients in the mipomersen group compared to 1 of 1 placebo-treated patient. The median intrahepatic triglyceride content was 24.4% in the mipomersen group, ranging from 0.8% to 47.3%. [22]

In a trial in which mipomersen was given to 39 patients with LDL-C ≥7.8 mmol/L or LDL-C ≥5.1 mmol/L plus CHD disease, on maximally tolerated lipid-lowering therapy, Mild-to-moderate injection site reactions were the most frequently reported adverse events with mipomersen. Mild-to-moderate flu-like symptoms were reported more often with mipomersen. Alanine transaminase increase, aspartate transaminase increase, and hepatic steatosis occurred in 21%, 13% and 13% of mipomersen treated patients, respectively. Adverse events by category for the placebo and mipomersen groups respectively were: total adverse events, 16(84.2%), 39(100%); serious adverse events, 0(0%), 6(15.4%); discontinuations due to adverse events, 1(5.3%), 8(20.5%) and cardiac adverse events, 1(5.3%), 5(12.8%). [24]

In a trial in which mipomersen was given to 83 patients with HeFH and coronary artery disease on maximally tolerated statin and LDL-C ≥2.6 mmol/L (≥100 mg/dL), Adverse events included injection site reactions and influenza-like symptoms. Five mipomersen patients (6%) had 2 consecutive alanine aminotransferase values ≥3 times the upper limit of normal at least 7 days apart; none were associated with significant bilirubin increases. Hepatic fat content increased a median of 4.9% with mipomersen versus 0.4% with placebo (P<0.001). [23]

## CONCLUSION

Mipomersen is an antisense apoB synthesis inhibitor that is currently in development for FH as a new treatment to lower apoB and LDL-cholesterol in patients at high risk of atherosclerotic CHD. Mipomersen is distributed mainly to the liver where it silences apoB mRNA, thereby reducing hepatic apoB-100 and giving rise to reductions in plasma total cholesterol, LDL-cholesterol, and apoB concentrations. Mipomersen has been shown to decrease apoB, LDL-cholesterol and Lipoprotein (a) in patients with heterozygous and homozygous FH on maximally tolerated lipid-lowering therapy. Furthermore, mipomersen has the potential to reduce the frequency of LDL apheresis.

The short-term efficacy and safety of mipomersen has been established, however, injection site reactions are common and concern exists regarding the long-term potential for hepatic steatosis and more safety studies on human liver function are required.

The delivery mode of injection could present a barrier to patient uptake and compliance. Alternative delivery mode is required that would make this drug available to a wider spectrum of patients who require to be treated to lower target levels of LDL-cholesterol either because current therapy is inadequate or that they cannot tolerate statins.

In summary, mipomersen given alone or in combination with standard lipid lowering medications shows promise as an adjunct therapy in patients with homozygous or refractory heterozygous FH at high risk of atherosclerotic CHD, who are not at target or are intolerant of statins. The long-term efficacy and safety and cost-effectiveness of mipomersen need to be demonstrated.

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