Research Article

Kynamro (Mipomersen): A Cholesterol Reducing Drug

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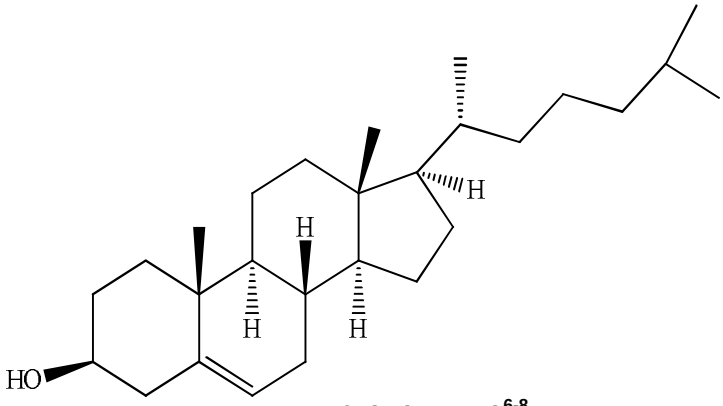
ABSTRACT

Hypercholesterolemia is characterized by high levels of low-density lipoprotein (LDL) cholesterol and it causes diseases such as tendon xanthomata, and premature atherosclerosis and coronary heart disease. Kynamro is a second-generation antisense oligonucleotide and it blocks the production messenger ribonucleic acid (mRNA) for apo B-100. It has been shown to decrease apoB, LDL-cholesterol in patients with heterozygous and homozygous hypercholesterolemia on maximally tolerated lipid-lowering therapy. It is distributed mainly to the liver. The most common adverse reactions are hepatic steatosis and injection site reactions. Kynamro given alone or in combination with standard lipid-lowering medications shows promise as an adjunct therapy in patients with homozygous or refractory heterozygous hypercholesterolemia at high risk of atherosclerotic CHD, who are not at target or are intolerant of statins.

Keywords: antisense oligonucleotide, apolipoprotein B, hypercholesterolemia, LDL-cholesterol.

INTRODUCTION

Cholesterol is a waxy, fat-like organic molecule. It is a modified steroid. It comes from two sources: body sources and food sources. It is essential to establish proper membrane permeability and fluidity. When cholesterol level increases in our body than the normal level then it is called as hypercholesterolemia. If there is too much cholesterol in the blood, some of the excess can become trapped in artery walls and it causes various heart diseases such as atherosclerosis or hardening of the arteries, chest pain or angina, heart attack etc [1-7].



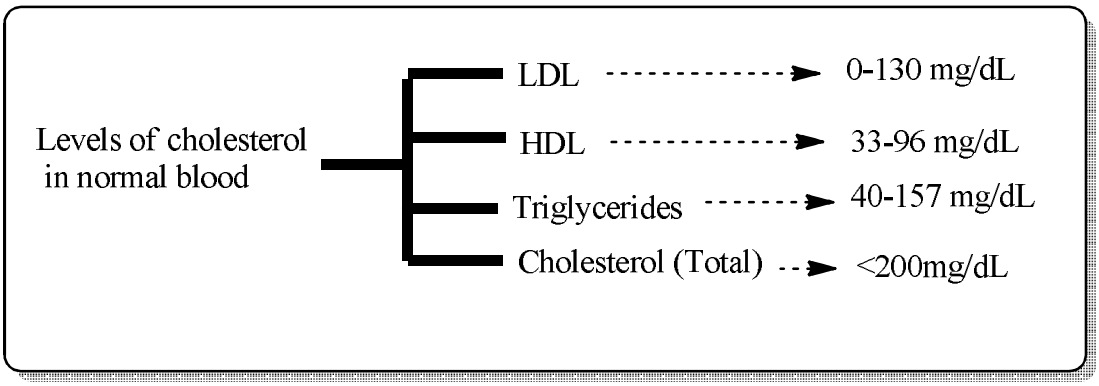
Structure of cholesterol [6-8]

Properties of cholesterol [8-10]

Properties	
Molecular formula	$C_{27}H_{46}O$
Molar mass	386.65 g/mol
Density	1.052 g/cm^3
Boiling Point	360^{0}C
Solubility	Soluble in water, acetone, benzene, chloroform, ethanol, ether, hexane, methanol

Types of cholesterol [11-13]

Types of cholesterol	Description
Low density lipoprotein (LDL)	It is called as 'bad'cholesterol. The higher level of LDL cholesterol in the blood, the greater the risk of heart disease. It carries cholesterol to tissues including arteries.
High density lipoprotein (HDL)	It is called as 'good' cholesterol. A low level of HDL cholesterol increase risk for heart disease. It carries cholesterol from tissue to the liver.
Triglycerides	A fat that circulates in blood and increase risk of heart disease.
Very low density lipoprotein (VLDL)	They are majorly composed of fats and lipids and have very little or all most no protein at all. Excess amount of VLDL cause heart disease.

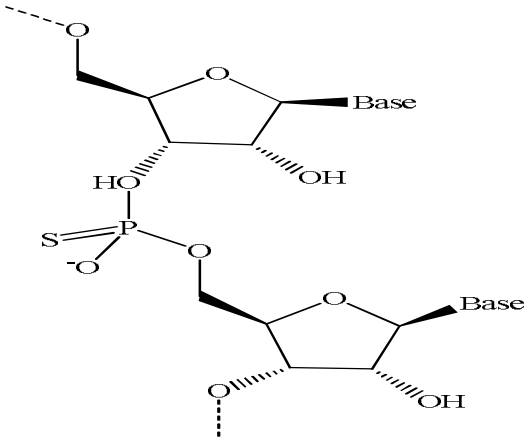


Levels of cholesterol in blood[11-16]

Factors affecting cholesterol in human body[17-19]

Risk factors	Description
Age and sex	Cholesterol level rise in aged people than younger. Before menopose, women tend to have lower total cholesterol levels than men of the same age.
Diabetes	Poorly controlled diabetes increases cholesterol levels
Exercise	For management of cholesterol levels exercise is needed. Regular exercise can lower LDL cholesterol and rise HDL cholesterol.
Weight	Excess weight tends to increase LDL level and decrease HDL cholesterol.
Diet	Saturated fat, trans fat, cholesterol diet make LDL level rise.
Heredity	High blood cholesterol can run in families.

Kynamro is an antisense oligonucleotide which is a very short fragment of DNA designed to block the production protein called apolipoprotein B. Apolipoprotein is the main component of LDL cholesterol. The U.S. Food and Drug Administration (FDA) has been approved kynamro on 28 January 2013 to treat inherited cholesterol disorder. It is administered by subcutaneous injection in a formulation with 0.9% sodium chloride and targets apo B-100 mRNA in the liver [18-21].



Structure of Kynamro

The molecular formula of Kynamro is $C_{230}H_{305}N_{67}O_{122}P_{19}S_{19}Na_{19}$ and the molecular weight is 7594.9 g/mol. The nucleotides are linked with phosphorothioate linkages rather than the phosphodiester linkages of RNA and DNA, and the sugar parts are deoxyribose in the middle part of the molecule and 2'-*O*-methoxyethyl-modified ribose at the two ends[23].

Mechanism of action

Kynamro is an antisense oligonucleotide and it consists of 20-mer 2´-O-methoxyethyl modified nucleotide complementary. It blocks the production messenger ribonucleic acid (mRNA) for apo B-100 which is the main component of LDL cholesterol. Kynamro forms a duplex with the targeted mRNA for apo B-100 and binds by Watson and Crick base pairing. The hybridization of kynamro to the cognate mRNA results in RNase H-mediated degradation of the cognate mRNA thus inhibiting translation of the apo B-100 protein and it reduces hepatic apo B, plasma total cholesterol, LDL-cholesterol and apo B concentrations in a dose and time-dependent manner [20, 24].

PHARMACOKINETICS

The various pharmacokinetics properties [25-27] of kynamro are following below-

Absorption

Kynamro has complete systemic absorption and peak concentrations of kynamro are typically reached in 3 to 4 hours after subcutaneous injection. The plasma bioavailability of kynamro ranged from 54% to 78% after following subcutaneous administration over a dose range of 50 mg to 400 mg.

Distribution

In plasma, greater than 85% of kynamro is bound to plasma proteins. It is rapidly and extensively distributed to tissues (volume of distribution in humans 48.3 L/kg). It has a distribution plasma half-life of approximately 2 to 5 hours.

Metabolism

Kynamro is metabolized in tissues by endonucleases to form shorter oligonucleotides that are then substrates for additional metabolism by exonucleases. It is not a substrate for CYP450 metabolism.

Excretion

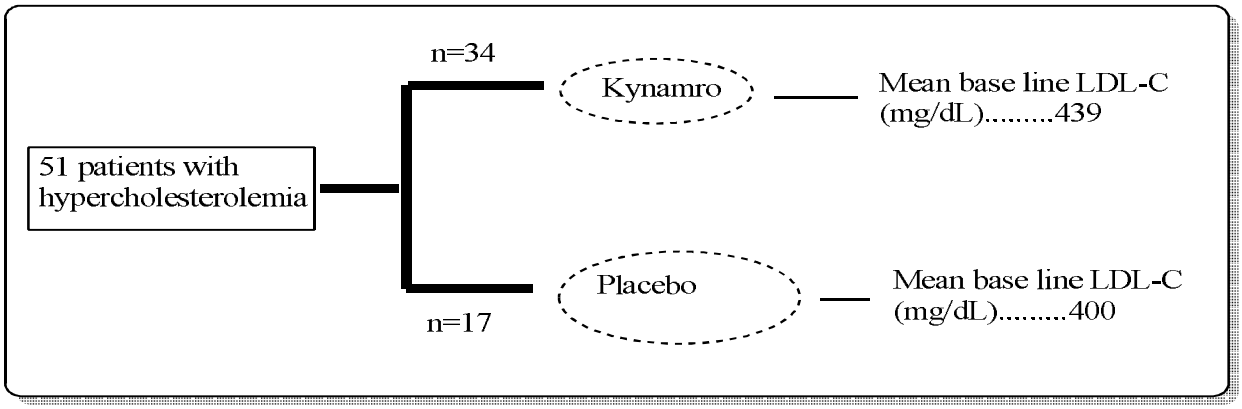
In the first 24 hours the urinary excretion of the drug is low. The elimination half-life for kynamro is approximately 1 to 2 months, after subcutaneous administration.

Drug Interactions

No clinically relevant pharmacokinetic interactions were reported between kynamro and warfarin, or between kynamro and simvastatin or ezetimibe.

CLINICAL TRIALS

In a clinical trials of kynamro, 51 patients with hypercholesterolemia were evaluated in a multinational, randomized [kynamro (n=34), placebo (n=17)], placebo controlled, 26-week trial. The recommended dose of kynamro is 200 mg once weekly as a subcutaneous injection given to the patients. The primary efficacy endpoint was percent change in LDL-C from baseline to Week 28. At Week 28, the mean and median percent changes in LDL-C from baseline were -25% ($p<0.001$) and -19%, respectively, for the kynamro group. The mean and median treatment difference from placebo was -21% (95% confidence interval [CI]: -33, -10) and -19%, respectively [22].



Clinical trial profile

DOSAGE AND ADMINISTRATION

Kynamro is available in a single-use vial or pre-filled syringe. The recommended dose of kynamro is 200 mg once weekly as a subcutaneous injection[20].

SUPPLIED, STORAGE AND HANDLING

Kynamro should be stored at 2-8^{0}C temperature and it should be protected from light. It should be supplied in single-use, 2 mL, clear glass vials or single-use, 1 mL, clear prefilled syringes with staked needles[20].

ADVERSE REACTIONS

The various adverse reactions [22] are following below-

Hepatotoxicity

Liver fat is increased in patients who received kynamro therapy than in patients receiving placebo. Increased hepatic fat causes liver disease, including steatohepatitis and cirrhosis. In clinical trials, the medium absolute increase in hepatic fat was 10% after 26 weeks of treatment from 0% of base line and the hepatic fat measured by magnetic resonance imaging (MRI). Patients should not consume alcohol in excess amount because it may increase liver fat and induce or exacerbate liver injury.

The concentration of serum transaminases such as alanin aminotransferase (ALT) and or aspartate aminotransferase (AST) is increased during the treatment of hypercholesterolemia patients with kynamro. Before initiation of treatment with kynamro, it is necessary to measure a full liver panel to include ALT, AST, total bilirubin and alkaline phosphatase.

Injection Site Reactions

Injection site reactions is the most common reported adverse reactions and it occurred in 84% of patients receiving kynamro versus 33% of placebo treated patients. Erythema (59%), pain (56%), hematoma (32%), pruritus (29%), swelling (18%) and discoloration (17%) are the most common injection site reaction. Injection site reactions did not occur with every injection.

Flu-like Symptoms

There are various flu-like symptoms including pyrexia, chills, influenza-like illness, myalgia, arthralgia, malaise or fatigue have been reported more frequently in patients receiving kynamro (29.9%) versus placebo (16.3%) in the pooled Phase 3 studies.

Immunogenicity

As per pooled Phase 3 trial, it is found that 38% of kynamro treated patients showed a positive result for anti-kynamro antibodies. Patients who are found positive in the anti-kynamro antibodies showed a similar result in patients who are found to be 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 kynamro therapy were found to be positive for anti-kynamro antibodies (35% with titers > 3200). Certain diseases like flu-like symptoms and the incidence of discontinuation of kynamro were seemed to be higher in antibody-positive patients and antibodies to kynamro were found to be associated at higher trough levels for the drugs. 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 kynamro with the incidence of antibodies to other products may be misleading.

SPECIAL CARE WITH SPECIAL POPULATIONS

Pregnancy

In case of pregnancy, kynamro should be used if clearly needed. During kynamro therapy, females should be advised to use effective contraceptives. There are no controlled data in pregnant women. Because animal reproduction studies are not always predictive of the human response, this drug should be used during pregnancy only if clearly needed. Reproduction and embryofetal development studies performed in mice at doses up to 87.5 mg/kg/week given by subcutaneous administration from mating through organogenesis and in pregnant rabbits given 52.5 mg/kg/week, show no evidence of impaired fertility or harm to the fetus at 2 (mice) to 5 (rabbits) times clinical exposure at a 200 mg/week therapeutic dose [22].

Nursing Mothers

Many drugs are excreted in human milk but it is not known whether kynamro is excreted in human milk. Before kynamro therapy of nursing mother, a decision should be made whether to discontinue nursing or discontinue the drug. Lactating rats administered

mipomerson at doses up to 70 mg/kg/week (3 times the anticipated systemic exposure from a 200 mg/week dose consumed less food while nursing. This correlated with reduced weight gain in the rat pups, and decreased pup survival.

Female's reproductive potentials-

Females of reproductive potential should use effective contraception during kynamro therapy. Special care should be provided for pregnant women during kynamro therapy because it may cause fetal harm.

Renal and hepatic impairment

Kynamro is not recommended in patients with severe renal impairment, clinically significant proteinuria or on renal dialysis because of the lack of clinical data and kynamro renal safety profile. The safety and efficacy of kynamro treatment in patients with known hepatic impairment have not been established. Kynamro is contraindicated in patients with clinically significant hepatic dysfunction, which may include persistent elevations of transaminases [22].

NONCLINICAL TOXICOLOGY

Impairment of Fertility, Carcinogenesis

Mipomersen sodium had no effect on fertility in mice at doses up to 87.5 mg/kg/wk (2 times clinical exposure at the 200 mg/wk dose based on body surface area comparisons).

In carcinogenicity study in mice, the mipomersen sodium was administered for up to 104 weeks at doses of 5, 20, 60 mg/kg/week. In this study incidence of hepatocellular adenoma, combined adenoma and carcinoma were significantly increases in female mice at 6o mg/kg/wk for both mipomersen sodium and mouse-specific analog. The incidence of hemangiosarcomas in female mice and fibrosarcomas of the skin/subcutis in male mice were also increases.

In carcinogenicity study in rats the mipomersen sodium was administered for up to 104 weeks at doses of 3, 10, 20 mg/kg/wk. There were statistically significant increases in the incidences of fibrosarcomas of the skin/subcutis and the combination of fibroma, fibrosarcomas and malignant fibrous histiocytoma of the skin/subcutis in female rats at 10 mg/kg/wk, at less than clinical exposure at the 200 mg/wk dose based on body surface area comparisons. It has been found that the rats of both sexes had significant increases in the incidence of malignant fibrous histiocytoma of the skin/subcutis at 20 mg/kg/wk (at clinical exposure at the 200 mg/wk dose based on body surface area comparisons[22].

Animal Pharmacology and/or Toxicology

Kidneys and liver are the principal targets organs and it represents the highest distribution of compound, and exhibit microscopic changes reflective of cellular uptake in macrophages.

Mipomersen has toxicological effect i.e spectrum of inflammatory changes in numerous organs including lymphohistiocytic cell infiltrates and increases in lymphoid organ weights, associated with increases in plasma cytokines, chemokines and total serum IgG [22].

MARKET ACCESS HISTORY

The ISIS Pharmaceuticals have discussed productive regulatory discussion regarding the mipomersen NDA filing on January 11, 2011. On March 29, 2012, ISIS Pharmaceuticals announced submission of U.S NDA for kynamro (mipomerson sodium) in Homozygous Familial Hypercholesterolemia (H_oF_H). The FDA submission of kynamro is supported by largest clinical trial conducted to date in the H_oF_H patient population. In the randomized, double-blind, placebo controlled, multicenter trial, significant reductions were observed in all atherogenic lipoproteins evaluated (including LDL-C, Apo B) for patient receiving kynamro who are already receiving a regimen of maximally tolerated lipid-lowering therapies including statins. FDA advisory committee recommends kynamro of H_oF_H. Genzyme had provided sufficient efficacy and safety data to support the marketing of kynamro for treatment of patient with H_oF_H. Finally FDA approves new drug orphan drug kynamro to treat cholesterol disorder on January 29, 2013 [28].

CONCLUSION

Kynamro is currently being studied in patients with mild to severe hypercholesterolemia as add-on therapy to other lipid-lowering therapy, as monotherapy in patients who are intolerant of HMG-CoA reductase inhibitors (statins) and who are at high risk for cardiovascular disease. This review provides an overview of the pathophysiology and current treatment options for familial hypercholesterolemia and describes novel therapeutic strategies focusing on mipomerson, an antisense apoB synthesis inhibitor.

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