INTRODUCTION:
Primary mature cystic teratomas are Familial Hypercholesterolemia (FH) is an autosomal dominant disorder characterized by elevated plasma levels of low density cholesterol (LDL-C), is caused by mutations in the LDL receptor gene. Total cholesterol levels are usually >500 mg/dL and can be as high as 1000 mg/dL. Most patients with homozygous FH present in childhood with cutaneous xanthomas on the hands, wrists, elbows, knees, heels, or buttocks. The devastating complication of homozygous FH is accelerated atherosclerosis, which can result in disability and death in childhood1.

Treatment is often complex and complicated. FH patients require Statins (HMG co-reductase inhibitors), in combination with the addition of a cholesterol absorption inhibitor and/or bile acid sequestrant. Nicotinic acid is also added sometimes. These drugs are given at higher doses and hence adverse effects by these drugs such as nausea, myalgia, liver damage, pigmentation (by niacin) are common 2.

Treatment is largely unsatisfactory, none of the currently available hypolipidemic drug alters natural history of the disease process considerably. There is an unmet need of drug development for this condition, and hope arrived with the discovery of Mipomersen, an antisense oligonucleotide molecule approved recently by FDA for familial hypercholesterolemia.

MECHANISM OF ACTION:
It is an antisense oligonucleotide; that targets apolipoprotein B. It is complimentary in structure to m-RNA of apolipoproteins B and reduces synthesis of apolipoprotein B, which is the cofactor of low density cholesterol 3, 4. The drug nucleotides are linked with phosphoro-thioate 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. These modifications make the drug resistant to degradation by nucleases, allowing it to be administered weekly.

PHARMACOKINETICS:
Following subcutaneous injection, peak concentrations of mipomersen are typically reached in 3 to 4 hours. The estimated plasma bioavailability of mipomersen following subcutaneous administration over a dose range of 50 mg to 400 mg, relative to intravenous administration, ranged from 54% to 78%. Mipomersen is highly bound to human plasma proteins (≥ 90%) at clinically relevant concentrations (1-8 μg/mL). It is given as 200 mg SC once weekly. Mipomersen has a distribution plasma half-life of approximately 2 to 5 hours. Mipomersen is not a substrate for CYP450 metabolism, and 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 urine7, 8.

FDA APPROVAL:
In January 29, 2013, approved (mipomersen sodium as an addition to lipid-lowering medications and diet to treat patients with a rare type of high cholesterol called homozygous familial hypercholesterolemia (HoFH)6.

The safety and effectiveness of mipomersen were evaluated in a clinical trial of 51 patients with HoFH. On average, levels of LDL-C fell by about 25 percent during the first 26 weeks in those receiving the drug. The FDA approved this drug with a Risk Evaluation and Mitigation Strategy (REMS) with elements to assure safe use, including prescriber and pharmacy certification, and documentation of safe-use conditions, which requires a prescription authorization form for each new prescription.

1. Department of Pharmacology, Saveetha Medical College, Chennai
2. Department of Pharmacology, Govt. Stanley Medical College & Hospital, Chennai.
ADVERSE EFFECTS, PRECAUTIONS, DRUG INTERACTIONS:

The most common adverse reactions in the clinical trial included injection site reactions, flu-like symptoms, nausea, headache and elevations in liver enzymes (serum transaminases). It carries a Boxed Warning on the serious risk of liver toxicity because it is associated with liver enzyme abnormalities and accumulation of fat in the liver, which could lead to progressive liver disease with chronic use. One of the differentiating feature of mipomersen is, it is not a substrate for CYP450. Hence so far no significant drug interactions noted in clinical trials 7, 8.

CONCLUSION:

The development of this antisense molecule is certainly a remarkable history in the development of hypolipidemic drugs. Long term effects is to be scrutinized in detail. The FDA has made it mandatory four postmarketing studies for this drug to assess for the presence of antibodies to ds-DNA in patients treated with mipomersen, a long-term registry of patients treated with mipomersen to determine the long-term safety and an enhanced pharmacovigilance program to monitor reports of malignancy, immune-mediated reactions, and hepatic abnormalities caused by this drug6.

REFERENCES:


CONFLICT OF INTEREST:

Dr.K.Vasanthira is a members of the editorial board, who has also authored this article was not involved in the selection , review and publication of this article.