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A Systemic Review on Resmetirom for Treatment of Non – Alcoholic Steatohepatitis

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A B S T R A C T

This systemic review provide an in depth evaluation of Resmetirom (Rezdiffra),a liver directed, selective thyroid hormone receptor beta agonist ,for the treatment of non –alcoholic steatohepatitis (NASH) .Resmetirom has shown promising results in reducing liver fat ,inflammation ,and fibrosis by targeting specific metabolic pathways .clinical evidence from phase 2 and phase 3 trials underscores its efficacy in improving liver histology and metabolic parameters ,making it a breakthrough in NASH therapy .The review further discusses challenges in NASH drug development and strategies for enhancing therapeutic outcomes , highlighting Resmetirom potential to transform the treatment paradigm for this progressive liver disease .

Keywords: Resmetirom, Rezdiffra, Non-alcoholic steatohepatitis, NASH, THR-beta agonist, fatty liver, fibrosis.

1.Introduction:

1.1 Hepatic steatosis:

The accumulation of excess fat, particularly triglycerides, within liver cells is known as hepatic steatosis.[1] This illness has two primary causes: Alcoholic fatty liver disease (AFLD) and non-alcoholic fatty liver disease (NAFLD). [(2)]

Pathophysiology of hepatic steatosis: Insulin resistance causes a number of changes in the body, including the development of fatty

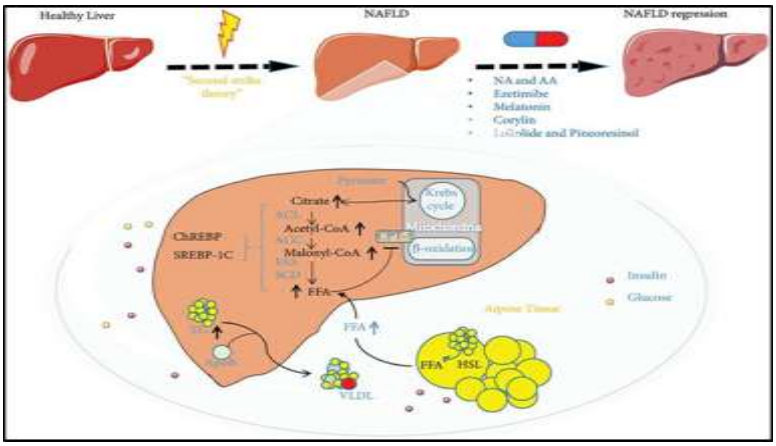

Fig 1:-Pathophysiology of Hepatic steatosis [4]

liver, or hepatic steatosis. As a result, triglycerides, or fat, accumulate in the liver. The prevalent theory holds that adipocytes, or fat cells, release more free fatty acids (FFAs) as a result of obesity and insulin resistance. FFA levels in the blood rise as fat cells enlarge and breakdown more triglycerides. Without limitations, the liver absorbs these FFAs; hence, the more FFAs present in the blood, the more the liver absorbs. Two Once within the liver, FFAs can be converted into triglycerides or burnt to produce ATP by one of two processes**.** For export from the liver, these triglycerides are either retained inside the liver cells or packaged into VLDL particles. Fat accumulation in the liver, known as hepatic steatosis, can result from problems with either of this processes.[3]

1.2 Cause of Hepatic steatosis:

1. Obesity
2. High blood pressure
3. High cholesterol level
4. Diabetes
5. Genetic condition
6. Autoimmune disease
7. Excessive alcohol consumption
8. Medications

1.3 Symptoms of Hepatic steatosis:

1. Extreme exhaustion or weakness
2. Nausea
3. Unexplained weight
4. Swelling in abdomen
5. Yellowish skin [5]

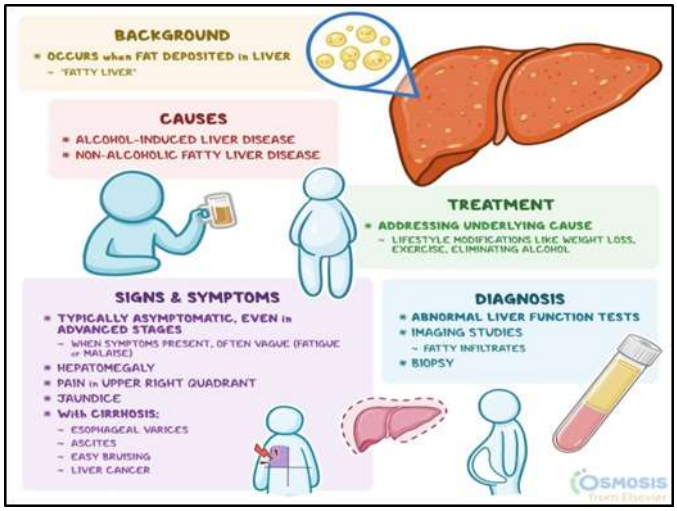

Fig 2:- Causes and Symptoms of Hepatic Steatosis [6]

1.4 Non alcoholic steatohepatitis:

The more severe and advanced kind of non-alcoholic fatty liver disease (NAFLD) is known as non-alcoholic steatohepatitis (NASH). In addition to inflammation and damage to the liver's cells (such as cell ballooning), it happens when the liver accumulates fat. Liver scarring (fibrosis) may or may not be a result. [(7)]

In 1980, Ludwig first established "non-alcoholic steatohepatitis" (NASH). Schaffner used the term "non-alcoholic fatty liver disease" (NAFLD) in 1986 to refer to a broad category of liver disorders associated with fat accumulation.

A number of metabolic problems, such as obesity, hypertension, elevated cholesterol, type 2 diabetes, thyroid dysfunction, and metabolic syndrome, are associated with non-alcoholic fatty liver disease (NAFLD). In order to identify non-alcoholic fatty liver disease (NAFLD), physicians must look for evidence of liver fat accumulation by imaging tests or tissue samples and rule out other potential reasons, such as excessive alcohol use, hereditary diseases, or drugs that can cause liver fat accumulation. [(8)]

The only kind of NAFLD that has the potential to worsen over time is NASH. NASH and NAFLD can present similarly, even if we are concentrating on NASH. NASH is frequently discovered by chance during testing and is associated with metabolic syndrome, polycystic ovarian syndrome, and sleep apnea. Hypopituitarism, hypogonadism, and hypothyroidism are among the various conditions that can coexist with NASH. It's crucial to understand that

even thin individuals without clear risk factors can develop NASH. Although it is uncommon, some persons with NASH may have moderate abdominal pain or fatigue. The majority of NASH patients do not exhibit any symptoms. Liver enzyme levels in NASH patients might range from normal to five times higher. In advanced cases, the AST to ALT ratio is usually less than 1. Other lab results may show elevated GGT, high cholesterol, or high blood sugar.[9]

2. Resmetirom:

Resmetirom (Rezdiffra) is a pill that targets the liver and activates a specific type of thyroid hormone receptor called THRβ. The FDA's approval of this drug is a big step forward for treating NASH (non-alcoholic steatohepatitis), especially after many previous attempts to develop effective drugs have failed. [10]

On March 14, 2024, the FDA gave conditional approval to Resmetirom, a drug to treat fibrotic (stage 2 or 3) MASH. MASH is a more advanced form of MASLD, a liver disease linked to metabolic problems. [(11, 12)]

So far, getting conditional FDA approval for a drug to treat MASH has been difficult, even though many drugs have gone through advanced stages of testing. [(13)]

A drug gets full FDA approval when it clearly helps patients with MASH. Since this can take a long time, the FDA can give conditional approval for drugs treating MASH with moderate to severe liver scarring (stage 2 or 3). This happens if the drug meets certain goals, such as reducing liver inflammation without making scarring worse, or improving scarring without making inflammation worse.[14]

2.1 Structure & Physical properties:

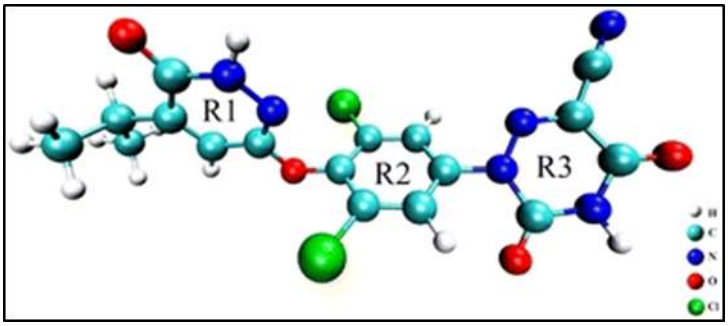

Fig.3:- 3D Structure of Resmetirom

1. **Molecular Formula :** $C_{17}H_{12}Cl_2N_6O_4$
2. **IUPACName:**2[3,5-dichloro-4-[(6-oxo-5-propan-2-yl-1H-pyridazin-3-yl)oxy]phenyl]-3,5-dioxo-1,2,4-triazine-6-carbonitrile
3. **Molecular weight:**435.2g / mol
4. **Category :**THR-β Agonist
5. **Dose:** Dosage based on actual body weight:

Less than 100 kg: 80 mg orally once a day

100 kg or greater: 100 mg orally once a day

6. **Description:** MGL-3196 has been tested in clinical trials for treating Non-alcoholic Steatohepatitis (NASH) and Heterozygous Familial Hypercholesterolemia (HeFH).
7. **Solubility:** low aqueous solubility below pH 6 and higher solubility above pH 7 (0.44 mg/mL at pH 7.04)
8. **Melting point :**321°C
9. **Brand name :**Rezdiffra
10. **Generic name :**Resmetirom
11. **Synonyms:**MGL-3196
12. **Storage :** Resmetirom should be stored properly to stay effective:
    1. Temperature: Keep it at room temperature, usually between 20°C to 25°C (68°F to 77°F).
    2. Humidity: Keep it away from too much moisture.

3. Light: Store it in a container that blocks light, away from direct sunlight.[25]

13. Half life: The median terminal plasma half-life of Resmetirom is about 4.5 hours.

14. Clearance: The steady-state apparent clearance (CL/F) of Resmetirom is 17.5 L/h. This means that, at steady-state, about 17.5 liters of the drug are cleared from the body every hour.

15. Indication: Resmetirom is used together with diet and exercise to treat adults with noncirrhotic non-alcoholic steatohepatitis (NASH) who have moderate to advanced liver fibrosis (stages F2 to F3). It should not be used in patients with decompensated cirrhosis.[15]

3. Mechanism of Action:

Thyroid hormones, like FT4 and FT3, help control how the liver processes fat. The thyroid hormone receptor-beta (THR-β) is the main receptor for these hormones in the liver. When this receptor is turned on, it helps reduce fat stored in the liver.

Many people with non-alcoholic fatty liver disease (NAFLD) also have low thyroid function, like in hypothyroidism. This makes hypothyroidism a risk factor for NAFLD. When the thyroid is underactive, it can cause problems with fat breakdown, leading to fatter going to the liver. This can cause insulin resistance in the liver and lead to more inflammation and scarring.

Resmetirom is a medicine that partially activates THR-β, helping to break down fats in the liver and reduce liver fat. It targets the liver more than other organs, like the heart and bones, making it safer for reducing liver fatty.[16]

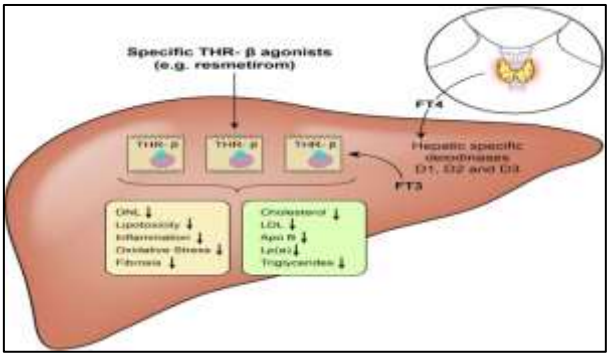

Fig 5:- Mechanism action of Resmetirom [17]

4. Synthesis Method of Resmetirom:

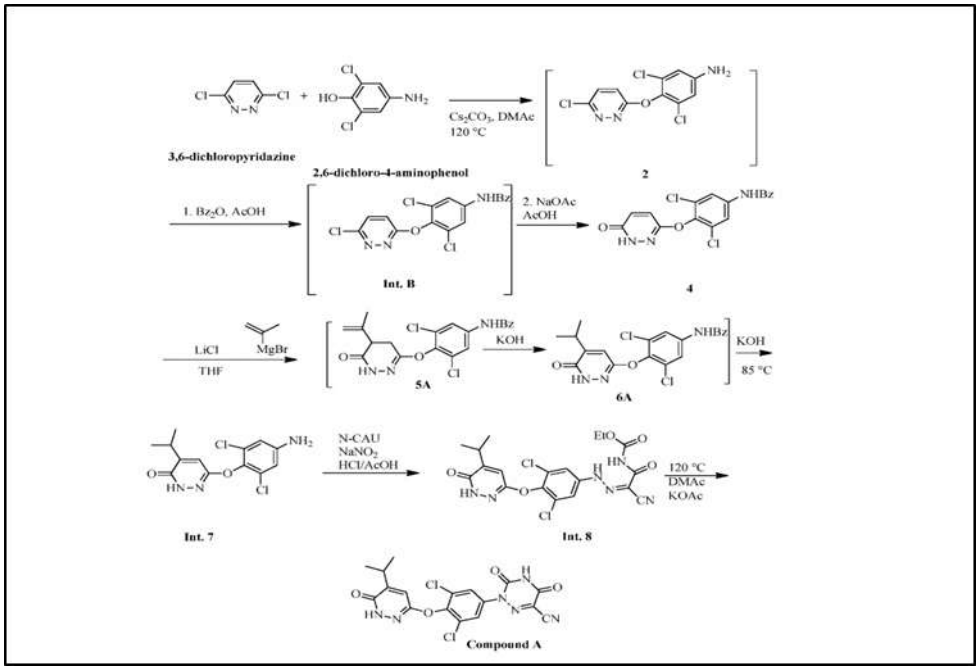

Fig 6:- Synthesis Method Of Resmetirom 1

Synthesis step of Resmetirom (Method -1):

1. **Initial Reaction:** In a 2 L round-bottom flask with stirring and a nitrogen (N_2) atmosphere, mix Int. 8 (89.3 g), DMAC (446 mL), and KOAc (20.0 g). Heat the mixture to 120 °C for 2 hours until the reaction is complete.

2. **Cooling and Precipitation:** Cool the mixture to 18 °C, add acetic acid (22.3 mL), then cool further to 8 °C. Add water (714 mL) over 1 hour to form orange slurry. Filter this slurry and let it rest overnight under N_2.

3. **Rinsing and Drying:** Rinse the solid with a 1:1 solution of acetone/water (445 mL) under vacuum, then transfer to a clean flask. Add ethanol (357 mL) and acetone (357 mL) and heat to 60 °C. Gradually add water (890 mL) while maintaining 55-60 °C. Cool to 25 °C, filter, and wash with ethanol/water solution (446 mL). Let it rest overnight under N_2, apply vacuum, wash with water (179 mL), and dry in a 45 °C vacuum oven to obtain 70.5 g of crude Compound A (Resmetirom) with 94.8% purity.

4. **Purification with MIBK(methyl isobutyl ketone):** Place crude Compound A(Resmetirom) (70.0 g) in a flask with MIBK (350 mL), heat to 50 °C for 2 hours, then cool to 23 °C. Filter, rinse twice with MIBK (35 mL each), and dry in a 45 °C vacuum oven to get 58.5 g of solid.

5. Final Recrystallization: Add ethanol (290 mL) to the solid in a flask, heat to reflux for 3.5 hours, and then cool to 25 °C. Filter and wash with ethanol (174 mL), then dry at 40 °C to yield 50.4 g of Compound a (Resmetirom) with 99.1% purity.

The final product is confirmed with 1H NMR analysis.[18]

5. Evaluation Parameter of Resmetirom:

5.1 Solubility:

Resmetirom's solubility varies depending on the solvent, pH, and temperature. In water, the solubility is influenced by pH. At a neutral pH of 7, its solubility is 0.1 mg/mL, which decreases to 0.05 mg/mL in acidic conditions (pH 5) and increases to 0.2 mg/mL in alkaline conditions (pH 9). This indicates that resmetirom is more soluble in alkaline environments. In organic solvents, the drug shows significantly higher solubility, dissolving at concentrations of 10 mg/mL in ethanol, 20 mg/mL in acetone, 5 mg/mL in methanol, and 50 mg/mL in DMSO. These values highlight that resmetirom dissolves more readily in solvents like DMSO and acetone. When tested in biological fluids, such as plasma and serum, its solubility is 0.05 mg/mL, while in saline; it is slightly higher at 0.1 mg/mL. Overall, Resmetirom's solubility increases in alkaline conditions (above pH 7) and decreases in more acidic conditions (below pH 5).[19]

5.2 Stability:

Resmetirom is stable under specific conditions, maintaining its chemical, pharmacological, and physical properties in controlled environments. Chemically, it is stable at room temperature (20-25°C) and under normal lighting conditions but begins to break down at high temperatures above 250°C. Pharmacologically, it remains stable in aqueous solutions with a pH range of 5-7 and in organic solvents such as ethanol and acetone. Physically, resmetirom is stable in its crystalline solid form, though it is moderately hygroscopic and can absorb some moisture from the air. These stability characteristics are important for its storage and handling.[20]

5.3 Melting Point:

Resmetirom has a melting point in the range of 187-190°C (369-374°F), with a more precise observed value of 189-190°C (372-374°F). This is the temperature range at which the solid transitions into a liquid. The melting point can be measured using methods such as differential scanning Calorimetry (DSC), which detects heat changes during the phase transition, and Thermogravimetric analysis (TGA), which measures weight changes associated with melting. These techniques ensure accurate determination of the melting point.[21]

5.4 Boiling Point:

Resmetirom has a boiling point of approximately 430-440°C (806-824°F), which is the temperature at which it transitions from a liquid to a vapour state. The boiling point can be determined using several methods. Distillation involves heating resmetirom until it vaporizes and measuring the temperature at that point. Thermogravimetric analysis (TGA) measures the weight loss of the substance as it vaporizes. Differential scanning Calorimetry (DSC) is another method that detects heat changes occurring during the vaporization process. These techniques help accurately determine the boiling point of resmetirom.[22]

5.5 Hygroscopicity:

Resmetirom is moderately hygroscopic, meaning it can absorb moisture from the air at a moderate rate. Under conditions of 60% humidity and 20°C, it can gain 10-20% of its weight within 24 hours. When exposed to higher humidity levels, such as 80% at 20°C, the weight gain increases to 20-30% over seven days. To measure the Hygroscopicity of resmetirom, several methods can be used, including gravimetric analysis, dynamic vapour sorption (DVS),

and inverse gas chromatography (IGC). These techniques help quantify the extent of moisture absorption and characterize its behaviour in different environments**.**[23]

6. Brand Product of Resmetirom:

6.1 Rezdiffra Tablet:

1. Medicine Name : Rezdiffra
2. API : Resmetirom
3. Dosage forms & strength: Tablets : 60 mg , 80mg,100mg
4. Storage: Store at room temperature between 68ºF to 77ºF (20ºC to 25ºC).
5. Manufactured By: Madrigal Pharmaceuticals, Inc.

6.2 Resiliva 80 mg:

1. Medicine Name : Resiliva 80
2. API: Resmetirom
3. Dosage forms & Strength: 80mg,100mg
4. Storage: Store at room temperature between 68ºF to 77ºF (20ºC to 25ºC).
5. Manufactured by**:** Everest pharma.[24]

7. Conclusion:

This review emphasizes the therapeutic potential of Resmetirom (Rezdiffra) as a promising treatment for non-alcoholic steatohepatitis (NASH), an area with significant unmet medical needs. Resmetirom selectively activates thyroid hormone receptor-beta in the liver, effectively reducing hepatic fat, inflammation, and fibrosis. Clinical trials have demonstrated its efficacy in improving liver histology and metabolic parameters. However, challenges such as long-term safety, patient adherence, and cost-effectiveness require further investigation. Continued research and real-world studies are crucial to establish Resmetirom's definitive role in the treatment paradigm of NASH and related metabolic disorder

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