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Resmetirom in Non Alcoholic Steatohepatitis (Nash).

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ABSTRACT :

NASH, which is characterized by hepatic inflammation, steatosis, and progressive fibrosis, is a leading cause of liver-related morbidity and mortality. There is an urgent need for novel, efficient treatments because there aren't many approved therapeutic options. Because it can target several pathophysiological pathways, including as inflammation and hepatic lipid buildup, Resmetirom, a selective thyroid hormone receptor-β (THR-β) agonist, has become a prospective therapy option for NASH. With an emphasis on Resmetirom's molecular mechanism of action, clinical trial results, difficulties, and future directions, this study attempts to provide an overview of the available data about the medication's safety and effectiveness in NASH.

Key Words : Non-alcoholic steatohepatitis (NASH), hepatic inflammation, Resmetirom, thyroid hormone receptor-β (THR-β), lipid accumulation.

Introduction:

Non-alcoholic steatohepatitis (NASH), a type of fatty liver disease that was first discovered in 1980, is typified by fibrosis, inflammation, and excessive liver fat accumulation. NASH falls under the more general heading of non-alcoholic fatty liver disease (NAFLD), which includes liver damage of various intensities. The combination of both inflammation and fibrosis in addition to the accumulation of fat makes NASH histologically different from a basic fatty liver, where fat builds up without either condition. NAFLD has been linked to a sedentary lifestyle, contemporary Western diet, and genetic predispositions. These result in oxidative stress and lipotoxicity, which in turn trigger the activation of intracellular stress kinases and apoptosis or necroapoptosis (NASH), which cause liver injury through insulin resistance and an excess of free fatty acids in hepatocytes.

Non-alcoholic steatohepatitis epidemiology:

Key risk factors for the development of non-alcoholic steatohepatitis (NASH) include the increasing incidence of insulin resistance, dyslipidemia, and obesity. About 82% of those with NASH are obese, 83% have hyperlipidemia, and 48% have type 2 diabetes, according to epidemiological studies. One of the liver disorders with the quickest rate of growth is NASH-induced cirrhosis. The chance of developing cirrhosis, liver failure, hepatocellular cancer, and ultimately mortality will rise if treatment is not received.

Pathophysiology of NASH :

Hepatic steatosis (fat accumulation), inflammation, and fibrosis are the hallmarks of non-alcoholic steatohepatitis (NASH), a complicated, progressive liver disease. Numerous elements contribute to the pathophysiology of NASH, such as oxidative stress, inflammatory reactions, and metabolic abnormalities.

1) Insulin resistance and hepatic lipid accumulation: Insulin resistance is the primary pathophysiological mechanism of nonalcoholic steatohepatitis (NASH). Increased levels of free fatty acids (FFAs) in the bloodstream are caused by insulin resistance. These FFAs are then transported to the liver, where they undergo esterification to become triglycerides. The initial stage of NASH, steatosis, is characterized by a buildup of fat and is frequently asymptomatic.

2) Lipotoxicity and Oxidative Stress: Triglycerides build up in hepatocytes, which causes mitochondrial β-oxidation to rise. They have the potential to induce oxidative stress, which harms DNA, lipids, and proteins found in cells. The increased amounts of saturated fatty acids, which are harmful to liver cells and are referred to as lipotoxicity, worsen this damage. Hepatocyte damage and cell death brought on by lipotoxicity trigger an inflammatory reaction.

Inflammation and Cytokine Release: A number of inflammatory pathways are activated in response to oxidative stress and hepatocyte damage. Pro-inflammatory cytokines such interleukin-6 (IL-6), interleukin-1β (IL-1β), and tumor necrosis factor-alpha (TNF-α) are released by the injured hepatocytes. These cytokines further prolong liver inflammation by attracting and activating immune cells such as neutrophils and Kupffer cells (liver macrophages).

Resmetirom:

Resmetirom (MGL-3196) is an oral active agonist of THR that is guided by the liver and is about 28 times more selective for THR-β compared to THR-α than triiodothyronine. It exhibits selective absorption into the liver, has low tissue penetration outside the liver, and is highly protein bound (>99%). Hepatocytes have a high expression of thyroid hormone receptor β (THR-β), which controls the liver's metabolic processes.

Resmetirom for Non-Alcoholic Steatohepatitis Treatment:

A THR-β agonist should ideally accomplish Three objectives:

1) decreased fibrosis, inflammation, and hepatic steatosis.

2) The hypothalamus-pituitary-thyroid axis, which controls serum thyroid levels, is unaffected by liver specificity.

3) The heart and bone/cartilage are protected from off-target THR-α effects by having high THR-β selectivity.

Resmetirom and other THR-β agonists are thought to activate THR-β, a nuclear hormone receptor that is prevalent in hepatocytes. A number of genes that support the intake of free fatty acids from external sources as well as increased production and uptake of internal free fatty acids from de Novo lipogenesis and lipophagy are thought to be modulated by activating THR-β. Mitophagy of diseased mitochondria and increased mitochondrial biogenesis boost the ability to manage and burn the elevated free fatty acid flow. While upregulated HMGCoA reductase produces more cholesterol, enhanced CYP7A1 and excretion boost bile acid production, and stimulation of LDL-R increases the liver's absorption of LDL. Consequently, LDL cholesterol levels fall while fatty acid β-oxidation, mitochondrial biogenesis, de novo lipogenesis, cholesterol, and bile acid production all rise. Another recognized downstream target of THR-β is SHBG, which transports androgens and oestrogens in blood and controls their access to target tissues. It may also be a biomarker of target engagement.

Safety and Adverse Effects:

Safety and Side Effects: Resmetirom's safety profile has been closely observed in clinical trials, despite its encouraging efficacy. The following adverse effects are most frequently reported:

1) Gastrointestinal Problems: During the early phases of treatment, nausea, diarrhea, and abdominal pain were prevalent.

2) Endocrine Effects: Some individuals had minor alterations in thyroid hormone levels as a result of Resmetirom's action on thyroid receptors.

3) Effects on the Liver: While Resmetirom improved liver function, some patients saw brief elevations in liver enzymes.

4) Cardiovascular Effects: Although less common, there were occasional reports of changes in heart rate and blood pressure, which are known risks associated with thyroid receptor modulation. Resmetirom was typically well tolerated, and the side effects were mostly controllable.

Challenges and Future directions:

Despite the encouraging outcomes, Resmetirom's development still faces a number of obstacles:

1) Long-term safety: Although short-term research has indicated that Resmetirom is well tolerated, further long-term safety information is still required, especially with reference to cardiovascular and thyroid health.

2) Patient heterogeneity: NASH is a diverse illness that progresses at different rates. To ascertain whether Resmetirom is beneficial in patients with concomitant diseases including diabetes and obesity as well as in all phases of NASH, more research is necessary.

3) Combination therapy: Given the multifactorial nature of NASH, combination medicines that target various pathways may yield better results. Research on the use of Resmetirom in conjunction with other NASH treatments is still ongoing.

Conclusion:

Resmetirom, which targets the liver's thyroid hormone receptor β, offers a novel mode of action and is a possible treatment option for patients with NASH. In early-phase trials, the medication has shown promise in lowering liver fat and enhancing biomarkers of liver fibrosis and damage. Long-term research is required to validate its clinical benefits and guarantee its safety in a larger patient population, even though its safety profile is generally favorable.

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