MASH CIRRHOSIS SYSTEMATIC REVIEW OF PHASE 2B TRIALS

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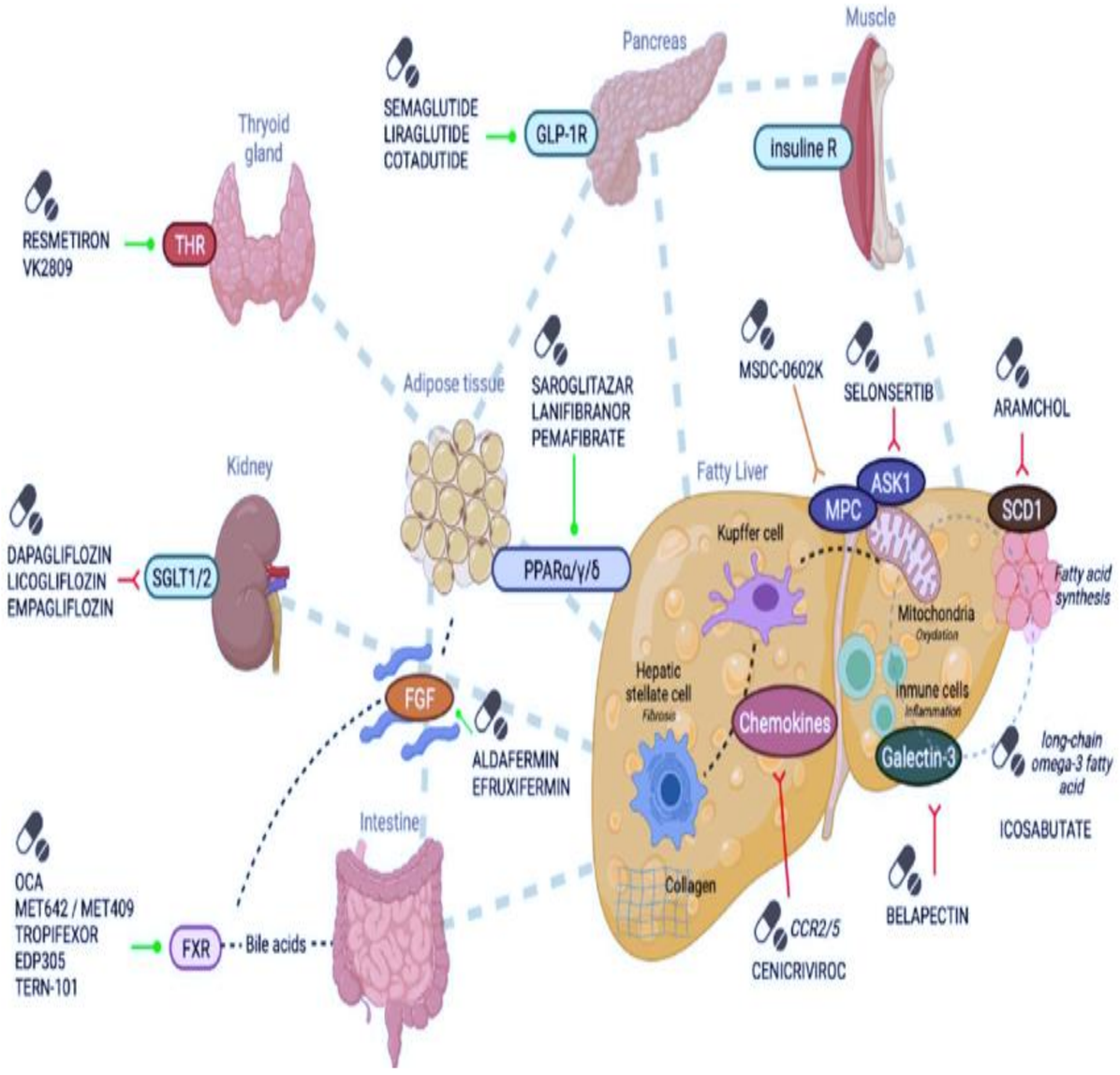

Trial	Drug	MOA
Study GT 026	GR-MD-02(Belapectin)	Inhibitor of Galectin-3 that reduces liver fibrosis and portal hypertension.
Native	Lanifibranor	A pan-PPAR agonist improves insulin sensitivity and macrophage activation and reduces liver fibrosis and inflammatory gene expression
Harmony	Efruxifermin	long-acting Fc-FGF21 fusion protein. fibroblast growth factor 21 (FGF21) is anti-fibrotic, improves metabolic status
Icona	Icosabutate	structurally enhanced omega-3 fatty acid molecule developed with the aim of achieving improved triglyceride (TG)-lowering efficacy
Tandem	Tropifexor (TXR) Cenicriviroc (CVC)	Tropifexor (TXR)- nonbile acid FXR agonist Cenicriviroc (CVC)- a potent inhibitor of C-C chemokine receptor types 2/5 (CCR2/5), has demonstrated antifibrotic and anti-inflammatory properties
Alpine2/3/4	Aldafermin	engineered analogue of the gut hormone fibroblast growth factor 19 (FGF19).
Falcon 1/2	Pegbelfermin (PGBF)	Long-acting glycopegylated (pegylated with the use of site-specific glycosyltransferases) fibroblast growth factor 21 (FGF21) analogue
Enliven	Pegozafermin	Long-acting glycopegylated (pegylated with the use of site-specific glycosyltransferases) fibroblast growth factor 21 (FGF21) analogue
Emminence	MSDC-0602K	Insulin desensitizer that binds mitochondrial pyruvate kinase

Introduction

- MAFLD/MASH is an umbrella term incorporating a spectrum of liver diseases, including fat deposition or steatosis without excessive alcohol consumption or any other causes of chronic liver disease.
- Further, it includes progressive stages of steatohepatitis, fibrosis, and finally cirrhosis and/or hepatocellular carcinoma.

Methodology

- 11 randomized control trials were included in this study
- All of the RCT's included in this systematic review are randomized double- blinded studies; 10 of the 11 are placebo-controlled, where the TANDEM trial compares tropifexor to cenicriviroc .
- All the studies only included patients with histological confirmation of NASH most required a biopsy performed within 6–months from screening.
- The NAS score was used as a screening tool in 5 of the 11 studies, and among these 5 studies the RCT's only included patients with a NAS> 4
- While most studies included patients with fibrosis stages 1,2, and 3, only 2 studies included patients with fibrosis 4.

Demographics

- For ten of the eleven studies, participant demographic information is available.
- The average age of participants is 54.3.
  In all the RCTs there were more Caucasian participants in both the placebo and treatment groups.
- The average prevalence of fatty liver in men was 26%, which was double that seen in women (13%).
- The RCT's included in this systematic review showed a female preponderance with as high as 80%
- BMI ranges between 32.5-38.7, which is unsurprising given that Obesity is a major driver of NAFLD and NASH around 50% of MAFLD patients and 80% of MASH patients present with obesity

Results

- Both the Emminence trial, with MSDC-0602K, and the Native trial, with Lanifibranor, are drugs that influence liver fibrosis by acting on the PPAR pathway. Although the PPAR agonist in the emminence trial failed to achieve its primary end point, patients treated with lanifibranor who had a decrease of at least 2 points in the SAF-A score without worsening of fibrosis were significantly higher among those who received the 1200-mg dose, but not among those who received the 800-mg.
- Study GT 026 assessed the efficacy of belapectin, an inhibitor of galectin-3, which was found to reduce liver fibrosis and portal hypertension in rats. There was no statistically significant difference between either concentration of belapectin and placebo when it came to reducing the hepatic vein pressure gradient (HVPG)
- The 52-week ICONA trial, trial was unable to demonstrate any statistically significant changes concerning the primary endpoint. The greatest treatment effect was seen in T2D patients, who responded to Icosabutate 600 mg with a NASH resolution rate of 35.5% (p=0.007 vs. placebo) and a NAS decrease of at least two points, compared to 4% in patients receiving a placebo.
- Members of the FGF superfamily, FGF19 and FGF21, have been extensively researched. Harmony, Enliven, and Falcon 1 and 2 trials focus on FGF21, while the Alpine trials include drugs that work on FGF19.
- The Harmony trial compared the efficacy of efruxifermin, long-acting FGF21 analogue, to placebo. The primary endpoint of the trial was to look for improvement in liver fibrosis score without worsening of NASH. eight (19%) of 43 patients in the placebo group met this endpoint versus 15 (36%) of 42 in the efruxifermin 28 mg group (RR 2·2 [95% CI 1·0–4·8]; p=0·033) and 14 (33%) of 43 in the efruxifermin 50 mg group (1·9 [0·8–4·3]; p=0·123).
- Falcon 1 and 2 are the other 2 trials that act via the FGF21 pathway. They study the effect of Pegbelfermin without fav. outcomes