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Review Article

Appraisal of resmetirom, a thyroid hormone receptor-β agonist, for treatment of non-alcoholic fatty liver disease

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Abstract

Hepatic hypothyroidism may play a role in the pathogenesis of non-alcoholic fatty liver disease (NAFLD) and its progression to nonalcoholic steatohepatitis (NASH). Resmetirom is an orally administered specific agonist of the thyroid hormone receptor-β (THR-β) recently approved for treatment of NASH. In a phase 3 clinical trial, called MAESTRO NASH, 966 patients with biopsy-confirmed NASH, were randomized to resmetirom 80 mg, 100 mg or matching placebo once-daily. After 52 weeks, NASH resolution without worsening of fibrosis was attained in 25.9%, 29.9%, and 9.7% in the 80-mg, 100-mg, and placebo groups, respectively. Fibrosis amelioration by at least one stage without worsening of the NAFLD activity score was achieved in 24.2%, 25.9% and 14.2% in patients in the 80-mg, 100-mg and placebo arms, respectively. The results of these 2 primary endpoints were similar in groups of subjects classified by fibrosis stage, NAFLD activity score, gender, age, and type 2 diabetes status. Results of imaging studies and serum markers of activity of NASH improved to a greater extent among resmetirom-treated patients compared with placebo. At 24 weeks, resmetirom reduced plasma levels of low-density lipoprotein cholesterol (LDL-C) by 13.6-16.3% versus no change with placebo. These changes were maintained at 52 weeks. Resmetirom also improved other atherogenic lipids such as apolipoprotein B and lipoprotein a but had no effect on plasma values of high-density lipoprotein cholesterol (HDL-C). Regarding thyroid function, the ratio of the biologically active free triiodothyronine (FT3) to the inactive reverse triiodothyronine (rT3) was increased with remetirom compared with placebo. Thyroid stimulating hormone (TSH) plasma concentrations were not altered by resmetirom. The commonest adverse effects of resmetirom: were transient diarrhea (27-33% vs 15% placebo), nausea 19-22% versus 12% with placebo, and vomiting 11% vs 5% with placebo. No increase in hyperthyroid symptoms was reported in relation to resmetirom. In conclusion, resmetirom is a promising agent for treatment of NASH. Long-term studies are needed to confirm its safety, efficacy, and impact on mortality in patients with NASH.

Keywords: resmetirom; hypothyroidism; fatty liver; nonalcoholic steatohepatitis; liver biopsy

Introduction

NAFLD is the most common cause of chronic liver disease affecting approximately 25% of persons globally [1]. Twelve to 14% of subjects with NAFLD may progress to NASH, which can lead to liver fibrosis, cirrhosis or liver carcinoma [1]. The pathophysiology of NAFLD is multifactorial and is closely related to obesity, type 2 diabetes and metabolic syndrome [1]. Another factor that is clearly implicated in the pathogenesis of NAFLD is "intrahepatic hypothyroidism" [2]. In fact, evidence derived from both epidemiological and interventional investigations strongly suggest that thyroid hypofunction may be closely linked to NAFLD. Thus, a population-based study from the USA has shown that low-normal thyroid function (TSH 2.5-4.5 mIU/L) and subclinical hypothyroidism were associated with an increase in prevalence of NAFLD diagnosed by liver ultrasound by 25% and 42%, respectively [3]. Furthermore, low thyroid function was an independent predictor of all-cause and cardiovascular mortality in patients with NAFLD, but not in those without NAFLD [3]. In a cross-sectional study from Spain using transient elastography for diagnosis of NAFLD, subjects with TSH levels ≥2.5 mIU/L had 1.5 times increased risk of NAFLD and 2.3 times increased risk of liver fibrosis compared with subjects with TSH <2.5 mIU/L [4]. In another cross-sectional survey from Germany, Ludwig et al [5] found increased prevalence of hepatic steatosis in subjects with reduced total T4 concentrations. Moreover, a meta-analysis of 13 studies concluded that both overt and subclinical hypothyroidism were independently correlated with NAFLD, with pooled odds ratio (OR) of 1.81 (95% CI, 1.3-2.5) and 1.63 (95% CI, 1.2-2.2), respectively [6]. On the contrary, hyperthyroidism was associated with lower risk of NAFLD (OR 0.85, 95% CI, 0.77-0.94, P<0.001) [7]. In a different investigation, higher FT3 levels were associated with decreased NAFLD (OR =0.26, 95% CI, 0.08-0.81, P=0.021) and lower hepatic fat content [8]. Furthermore, interventional studies have shown that levothyroxine therapy (median dose 75 mcg/d) decreased prevalence of NAFLD by 50% in patients with subclinical hypothyroidism with TSH levels

≥10 mIU/L [9]. Small-dose levothyroxine therapy (median dose 18 mcg/d) modestly reduced intrahepatic lipid content evaluated by magnetic resonant imaging (MRI) spectroscopy by absolute value of 2% and relative value of 12% [10]. Meanwhile, few observational studies did not find an association between hypothyroidism and NAFLD, likely due to the heterogeneous nature of NAFLD and differences in population characteristics [11,12].

Mechanistic links between hypothyroidism and nonalcoholic fatty liver disease

The close link between thyroid hormones and NAFLD may be explained by the well-established beneficial effects of thyroid hormones, particularly the biologically active T3, on lipid metabolism. Thus, T3 increases clearance of low-density lipoprotein cholesterol (LDL-C) via induction of LDL-C receptors in hepatocytes leading to a decrease in plasma levels of LDL-C [2]. In addition, T3 stimulates free fatty acid oxidation and hepatic lipase activity, which results in decreased fat accumulation in the liver [2]. Therefore, "intrahepatic hypothyroidism' may play a central role in the development and clinical consequences of NAFLD by promotion of hepatic fat accumulation and atherogenic lipid profile. Activity of thyroid hormones in the liver is controlled by 2 enzymes, deiodinase 1 (D1) and deiodinase 3 (D3) that work in concert to maintain hepatic thyroid homeostasis [2]. D1 converts the prohormone T4 to the biologically active T3, whereas D3 inactivates T4 and T3 by converting them to the inert metabolite rT3 and diiodothyronine (T2) [13]. The seminal experiments of Bohinc et al [14] have shed the light on the mechanisms underlying intrahepatic hypothyroidism by showing that compared with healthy subjects, liver biopsy specimens from patients with NAFLD exhibited decreased expression of D1 and increased expression of D3 leading to decreased T3, elevated rT3 and decreased T3/rT3 ratio [14]. Moreover, the degree of down regulation of D1-expression and upregulation of D3-expression occurred in parallel to the fibrosis stage [14].

Rationale of using resmetirom for treatment of NAFLD

Thyroid hormone action is mediated through 2 nuclear receptors: thyroid-hormone receptor-α (THR-α) and THR-β [15]. THR-α is the predominant isoform present in heart, bone, muscles, and gastrointestinal tract, whereas THR-β is the main isoform in the liver and kidney [15]. Indeed, individuals with a mutation of the THR-β gene had increased hepatic fat content compared with their first-degree relatives of similar age and weight [16]. Therefore, there was need to design a drug that stimulates THR-β to mimic the beneficial actions of thyroid hormones on lipid metabolism in the liver. In the meantime, it was crucial that this drug should lack any activity on the isoform THR-α to avoid any deleterious actions of thyroid hormones on heart and bones such as arrythmias and fractures. Resmetirom (*Rezdiffra*) is a THR-β agonist that is 28 times more selective in binding to THR-β than THR-α [17]. Therefore, resmetirom should virtually has no harmful extrahepatic thyroid effects. In addition, after oral administration, the drug uptake by the liver occurs via hepatic transporters [18]. Early studies in healthy volunteers lasting for 2 weeks showed significant effects of resmetirom in reducing plasma concentrations of LDL-C by 30%, apolipoprotein B by 24% and triglycerides by 60% without safety concerns [18]. This was followed by a phase 2 clinical trial and 36 week-extension that showed promise of resmetirom in reducing hepatic fat and reversing hepatic abnormalities with good tolerance to the drug [19,20]. This achievement prompted the launch of the phase 3 MASTERO clinical program that consisted of 4 trials to support approval of resmetirom by regulatory agencies [21]. Two of these 4 trials were published, the first trial included the initial 52-week phase of the MAESTRO-NASH trial and the second was MAESTRO -NAFLD-1 trial [22,23]. The main purpose of this article is to provide an appraisal on the efficacy and safety of resmetirom as a potential new treatment for patients with NASH.

Efficacy of resmetirom

The principal objective of the MAESTRO-NASH trial was to evaluate efficacy of resmetirom in patients with biopsy-confirmed NASH and fibrosis (F) stage of F1B, F2, or F3 [22]. The trial was randomized, double-blind, placebo-controlled and multinational [22]. Results of the initial 52 weeks were recently released but the planned follow-up should last 54 months [22]. Patients (n=966, mean age 56.6 years, 44% males) were mostly Whites (89%), obese (mean body mass index 35.7 kg/m2) with a high prevalence of metabolic diseases: hypertension 78%, dyslipidemia 71%, type 2 diabetes 67% [22]. Most patients had fibrosis stage F3 NASH (approximately 62%) followed by stage F2 (approximately 33%). Subjects were randomized into 3 almost equal groups to receive resmetirom 80 mg once daily, 100 mg once daily, or matching placebo [22]. Liver biopsy was performed at baseline and at 52 weeks (and a third biopsy will be performed at the end of follow-up at 54 months). The MAESTRO-NASH trial had 2 primary end points: NASH resolution with no worsening of fibrosis and reduction in fibrosis by at least one stage with no worsening of the NAFLD activity score [22]. After 52 weeks, NASH resolution with no worsening of fibrosis was achieved in 25.9%, 29.9% and 9.7% in patients randomized to resmetirom 80 mg, 100 mg, and placebo, respectively; P<0.001 for both resmetirom doses versus placebo [22]. Regarding the second outcome, improvement of fibrosis by ≥1 stage with no worsening of the NAFLD activity score was attained in 24.2%, 25.9% and 14.2% in patients receiving resmetirom 80 mg, 100 mg, and placebo respectively; P <0.001 for both resmetirom doses versus placebo [22]. These results were generally consistent across different subgroups classified by fibrosis stage and NAFLD activity score at baseline, diabetes status, age and gender [22].

Effects on plasma lipids

A key secondary end point of the MAESTRO-NASH trial was the percent change from baseline in directly measured LDL-C levels at week 24 [22]. Compared with baseline, there were reductions in plasma LDL-C levels by -13.6% in the 80-mg group, -16.3% in the 100-mg group versus no change in placebo (0.1%) at week 24; P < 0.001 for both comparisons with placebo [22]. In addition, there were significant reductions in plasma concentrations of triglycerides (-22 to -23% in resmetirom arms vs -3% with placebo), apolipoprotein B (-17 to -20% versus 1% increase in placebo), lipoprotein a (-30 to -36% vs -1% with placebo). These changes were maintained at 52 weeks [22]. Differences in HDL-C levels between resmetirom and placebo were not significant [22].

Effects on liver enzymes and other markers of liver inflammation

Use of resmetirom was associated with significant dose-related decrease in levels of liver enzymes. Thus, relative to placebo there were reductions in alanine aminotransferase, aspartate aminotransferase and gamma-glutamyltransferase with the 100-mg dose by 26%, 25%, and 35%, respectively [22]. Moreover, plasma levels of cytokeratin-18 decreased and those of adiponectin increased consistent with a reduction in severity of NASH [22,23].

Imaging studies

Results of imaging studies were in line with amelioration in hepatic histology both resmetirom groups. Thus, there was significant decrease in hepatic fat by 26.7% with the 80 mg-dose and 37.9% with 100 mg-dose versus placebo at 52 weeks as evaluated by magnetic resonant imaging-Proton Density Fat Fraction (MRI-PDFF) [22]. Similar trend was observed in liver stiffness as measured by vibration-controlled transient elastography (Fibroscan) at week 52 [22]. Moreover, there was reduction in liver volume by 21-25% at week 52 with resmetirom and no change with placebo [22]. Both doses of resmetirom led to an average reduction of approximately 6% in spleen volume versus an increase 3% with placebo at 52 weeks [22].

Effects of resmetirom on thyroid hormones

At 52 weeks, circulating levels of rT3, the inactive metabolite of T4, were reduced with resmetirom by approximately 20-24% versus an increase by 4% with placebo [22,23]. Likewise, the ratio of FT3/rT3 was increased (by 0.06-0.07 from a baseline of 0.17-0.18) by resmetirom compared with no change with placebo [22]. Significant reductions in FT4 by approximately 10-20% relative to placebo were demonstrated with resmetirom administration [22,23]. Meanwhile, no differences in FT3 or TSH levels were demonstrated between resmetirom and placebo groups [22,23]. Taken together, if these hormonal changes occur at the level of intrahepatic circulation, they suggest enhancement of conversion of T4 by resmetirom to its active hormone T3 rather than to its inactive metabolite rT3 restoring therefore thyroid hepatic

homeostasis. While the decrease in circulating FT4 plasma levels was statistically significant, it was unlikely to be clinically significant because TSH, an extremely sensitive parameter to any minor changes in thyroid function, remained unchanged. In addition, FT4 plasma levels remain within normal range. Interestingly, the above thyroid hormonal changes were similar in the subgroup of patients with hypothyroidism at baseline, which represented 13% of the AESTRO-NASH population [22]. Unfortunately, the authors did not mention if there were more frequent adjustments in levothyroxine doses in the resmetirom group versus placebo group [22,23].

Effect of resmetirom on quality of life

In a phase 2 study Younossi et al [24] evaluated the effects of resmetirom on health-related quality of life (HRQL) in patients with biopsy-proven NASH. They found that 54 of 116 patients (46.6%) had response to resmetirom defined as a decrease of ≥30% of liver fat by MRI. Responders had significant amelioration in HRQL compared with placebo, whereas resmetirom non-responders did not have change in HRQL [24]. The improvement in HRQL among resmetirom responders included improvement in physical functioning and bodily pain [24]. The benefits were largely independent of weight changes and were evident early after 12 weeks of therapy and lasted to the end of the study at 36 weeks [24]. However, this study used a general health survey, the SF-36 health survey, and not a specific instrument such as Chronic Liver Disease Questionnaire-NASH [24]. Another phase 2 trial by Harrisson et al [19] did not detect significant difference in QOL between resmetirom-treated patient (n=78) compared with placebo (n=38) after 36 weeks of intervention (type of QOL questionnaire was not mentioned). Nevertheless, HRQOL was evaluated as secondary endpoint in the larger MAESTRO-NASH trial but results were not released as of date of writing this paper [22].

Safety of resmetirom

The main objective of the randomized, placebo-controlled double-blind MAESTRO-NAFLD-1 trial was to study the safety of resmetirom (80 mg/d and 100 mg/d) over 52 weeks of follow-up [23]. The commonest adverse effect of resmetiron was diarrhea occurring in 23.5-31.2% of patients compared with 13.8% with placebo [23]. Nausea was the second frequent adverse effect reported by 11.9-18.2% of resmetirom-treated patients versus 7.9% of subjects receiving placebo [23]. Diarrhea and nausea occurred more frequently in the first 12 weeks of treatment. Beyond 12 weeks, the incidence of these adverse effects was similar to placebo [23]. Diarrhea was transient with a median duration of 15-20 days [23]. Discontinuation rates due to adverse effects were 3.1%, 2.4% and 1.3% in the resmetirom 100 mg/d, 80 mg/d and placebo, respectively [23]. Gastrointestinal adverse effects were also the commonest cause for study discontinuation [23].

Adverse effects of specific interest

It was essential to exclude any adverse effects that could be potentially related to systemic hyperthyroid effects of resmetirom, namely increase in heart rate, arrythmias, and fractures. In that respect, data up to 52 weeks derived from both MAESTRO-NAFLD-1 and MAESTRO-NASH trials were reassuring [22,23]. Thus, no increase in heart rate, arrythmias, cardiovascular events, or fractures were reported in association with resmetirom [22,23]. Likewise, no significant effect on weight or glycemic parameters was observed with remestirom [22,23].

Advantages of resmetirom

Despite the substantial burden of NASH, there are no approved pharmacologic agents for its treatment. In fact, several drugs were rejected recently by the Federal Drug Administration (FDA) due to lack of efficacy and safety [25]. Hence, there is an urgent need for an effective and safe medication for NASH. Resmetirom is orally administered once daily that shows clear benefits in patients with NASH based on hepato-histological, imaging, and laboratory data. Overall, resmetirom is well-tolerated. It is reassuring that resmetirom lacked the undesirable systemic hyperthyroid symptoms and signs at least up to 52 weeks of use. Interestingly, the positive effects in reducing atherogenic plasma lipids is another advantage given the fact that dyslipidemia prevails in patients with NASH and that cardiovascular disease is a major cause of death [1]. Indeed, the unique anti-lipidemic mechanism of action of resmetirom makes it a useful add-on therapy to other lipid-lowering drugs. In a phase 2 trial including 113 patients with heterozygous familial hypercholesterolemia and high LDL-C levels (131-137 mg/dl at baseline) despite taking high-intensity statins (82%) and ezetimibe (67%), resmeterom lowered LDL-C by 18.8% after 12 weeks versus placebo [26]. Preliminary economic data suggest that resmetirom is a potentially cost-effective drug for patients with NASH and liver fibrosis compared with placebo from a US commercial payer perspective [27].

Limitations of resmetirom

Resmetirom may be considered of only mild to moderate efficacy since NASH resolution occurred in approximately 26-30% of resmetirom-treated patients compared with 10% of placebo-treated subjects after 1 year [22]. Many exclusion criteria in the MAESTRO-NASH limited generalization of the trial results, e.g. exclusion of patients with hemoglobin A1c > 9.0% and patients with liver cirrhosis (fibrosis stage 4) [22]. In addition, minority groups were not well represented in the MAESTRO-NASH trial [22]. Long-term safety and efficacy of resmetirom beyond 52 weeks have yet to be studied.

Conclusions and current needs

Accumulating evidence suggests that intrahepatic hypothyroidism contributes to the pathophysiology of NAFLD. Resmetirom is a thyroid hormone receptor agonist that specifically activates the isoform β which mediates beneficial actions of thyroid hormones with respect to hepatic lipid metabolism. Resmetirom improved NASH histology and inflammation and was well-tolerated over 52 weeks. Patients with NAFLD should be screened for hypothyroidism by measuring TSH annually. If hypothyroidism is confirmed it should be treated even if subclinical in view of the positive results of levothyroxine therapy on NAFLD [9,10]. The MAESTRO-NASH trial is currently in its second phase and continues blinded for 54 months of follow-up. It will report a composite clinical outcomes that consist of: all-cause mortality, liver transplant, histological progression to cirrhosis, and increase in model for end-stage liver disease (MELD) score from <12 to ≥15) in addition to its long-term safety [28]. These pending data should establish the role of resmetirom for the management of NASH. *At present, resmetirom is approved under "accelerated approval" for treatment of NASH with moderate to advanced liver fibrosis [29]. Its continued approval depends on results of the ongoing second phase of the MAESTRO-NASH trial.*

Conflict of interest

The authors do not conflict of interest to declare

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