Chiglitazar: Is a 'pan' approach better for MASLD?

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> Metabolic dysfunction-associated steatotic liver disease (MASLD) represents a growing public health challenge, often progressing to more severe forms like metabolic dysfunction-associated steatohepatitis (MASH) and cirrhosis. Effective therapeutic strategies are urgently needed to halt or reverse this progression, particularly in patients with co-existing metabolic derangements. The field has long sought agents that can address the complex interplay of steatosis, inflammation, and insulin resistance that defines MASLD.1
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> A recent Phase II, randomized, double-blind, placebo-controlled study, published in Hepatology, evaluated chiglitazar, a peroxisome proliferator-activated receptor (PPAR) pan-agonist, in MASLD patients exhibiting both hypertriglyceridemia and insulin resistance. The trial aimed to determine if targeting multiple metabolic pathways simultaneously could offer a meaningful clinical benefit.1

KEY TAKEAWAYS

- The Pivot: Chiglitazar, a PPAR pan-agonist, demonstrated efficacy in reducing liver fat and improving insulin sensitivity in MASLD patients with specific metabolic comorbidities.
- The Data: Liver fat content, measured by MRI-PDFF, decreased by 35.2% from baseline in the chiglitazar group (P=.001 vs placebo).
- The Action: While promising, chiglitazar remains an investigational therapy; clinicians should continue to manage MASLD with lifestyle interventions and existing therapies until further data and regulatory approvals are secured.

MASLD, previously known as non-alcoholic fatty liver disease (NAFLD), is characterized by excessive fat accumulation in the liver, not due to alcohol. Its prevalence is rising globally, mirroring the epidemics of obesity, type 2 diabetes, and metabolic syndrome. The disease spectrum ranges from simple steatosis to MASH, which carries a significant risk of progression to advanced fibrosis, cirrhosis, and hepatocellular carcinoma. Current management primarily relies on lifestyle modifications, but these are often insufficient for many patients, leaving a substantial unmet need for pharmacological interventions.1

Chiglitazar is a PPAR pan-agonist, meaning it activates all three PPAR subtypes: alpha, gamma, and delta. PPAR-alpha activation primarily influences lipid metabolism, reducing triglycerides and increasing high-density lipoprotein cholesterol. PPAR-gamma is a key regulator of adipogenesis and insulin sensitivity, improving glucose uptake in peripheral tissues. PPAR-delta plays a role in fatty acid oxidation and energy expenditure. The rationale for a pan-agonist in MASLD with hypertriglyceridemia and insulin resistance is to simultaneously address multiple facets of metabolic dysfunction that drive liver pathology.1

Trial Design and Patient Cohort

The Phase II study enrolled 240 adult patients diagnosed with MASLD, confirmed by liver biopsy or imaging, who also presented with hypertriglyceridemia (fasting triglycerides ≥1.7 mmol/L or 150 mg/dL) and insulin resistance (HOMA-IR ≥2.5). Investigators excluded patients with other causes of liver disease, significant alcohol consumption, or advanced cirrhosis. The trial randomized participants 1:1:1 to receive either chiglitazar 50 mg once daily, chiglitazar 100 mg once daily, or placebo for 24 weeks. All patients received standard lifestyle advice throughout the study duration.1

The primary endpoint was the relative change in liver fat content from baseline to week 24, as measured by magnetic resonance imaging proton density fat fraction (MRI-PDFF). Secondary endpoints included changes in liver enzymes (ALT, AST), markers of insulin resistance (HOMA-IR, fasting glucose, fasting insulin), lipid profiles (triglycerides, LDL-C, HDL-C), and body weight. Safety and tolerability were also key considerations, with adverse events monitored throughout the study period.1

The Numbers on Efficacy

Chiglitazar demonstrated a statistically significant reduction in liver fat content. Patients receiving chiglitazar 50 mg experienced a mean relative reduction in liver fat of 35.2% from baseline (95% CI, 30.1-40.3; P=.001 vs placebo), while the 100 mg group saw a 38.7% reduction (95% CI, 33.5-43.9; P<.001 vs placebo). The placebo group, in contrast, showed only a 5.1% reduction (95% CI, 0.2-10.0). This indicates a clear dose-response trend, though both active arms were superior to placebo.1

Beyond liver fat, chiglitazar also improved markers of insulin resistance. HOMA-IR decreased by 28.5% in the 50 mg group (95% CI, 23.0-34.0; P=.003 vs placebo) and by 31.9% in the 100 mg group (95% CI, 26.5-37.3; P<.001 vs placebo). Fasting insulin levels followed a similar pattern, declining by 25.0% and 28.1% respectively in the active treatment arms (P=.005 and P=.002 vs placebo). These improvements in insulin sensitivity are critical, as insulin resistance is a central driver of MASLD pathogenesis.1

The drug also had a favorable impact on lipid profiles, consistent with its PPAR pan-agonist mechanism. Triglyceride levels decreased by 22.3% in the 50 mg group (95% CI, 17.1-27.5; P=.004 vs placebo) and by 26.8% in the 100 mg group (95% CI, 21.5-32.1; P<.001 vs placebo). HDL-C levels increased modestly, by 8.5% and 10.2% respectively (P=.01 and P=.008 vs placebo). LDL-C levels remained largely unchanged across all groups. These lipid improvements are particularly relevant for the study population, which specifically included patients with hypertriglyceridemia.1

Safety and Tolerability Profile

Chiglitazar was generally well-tolerated. The most common adverse events (AEs) reported were mild to moderate peripheral edema, occurring in 12% of patients in the 50 mg group and 15% in the 100 mg group, compared to 4% in the placebo group. This is a known class effect of PPAR-gamma agonists. Weight gain was also observed, with a mean increase of 1.8 kg in the 50 mg group and 2.3 kg in the 100 mg group, versus 0.5 kg in the placebo group. No cases of severe hypoglycemia were reported, and liver enzyme elevations were infrequent and transient, not leading to study discontinuation.1

Serious adverse events occurred in 3% of patients in the chiglitazar 50 mg group, 4% in the 100 mg group, and 2% in the placebo group, with no clear pattern suggesting a drug-related causality. Discontinuation rates due to AEs were low, at 5% for the 50 mg group and 6% for the 100 mg group, compared to 3% for placebo. The safety profile appears consistent with other PPAR agonists, requiring careful monitoring for fluid retention and weight changes.1

Where it Falls Short

The obvious caveat is the Phase II nature of this study. While the data on liver fat reduction and metabolic improvements are compelling, a 24-week duration is insufficient to assess long-term clinical outcomes such as progression to cirrhosis, liver-related events, or all-cause mortality. These are the hard endpoints that ultimately define a drug's value in MASLD. The study was also not powered to detect histological improvements in MASH, which is a critical step in drug development for this disease. Liver biopsy, the gold standard for MASH diagnosis and staging, was not a mandatory endpoint for all participants, relying instead on MRI-PDFF for liver fat quantification.1

The patient population, while well-defined by hypertriglyceridemia and insulin resistance, may not fully represent the broader MASLD spectrum. Whether these benefits extend to patients without significant hypertriglyceridemia or with more advanced fibrosis remains an open question. The observed weight gain, though modest, is a concern in a patient population already struggling with metabolic health. Future studies will need to address the balance between metabolic benefits and potential adverse effects like fluid retention and weight increase, particularly in a chronic treatment setting.1

The mechanism of action, while broad, also presents challenges. Pan-PPAR agonists have historically faced hurdles in development due to off-target effects or an unfavorable risk-benefit profile. The modest increase in HDL-C, for example, is less pronounced than seen with selective PPAR-alpha agonists, and the weight gain is a known issue with PPAR-gamma activation. Still, the overall metabolic improvements are encouraging. The next phase of development will need to clarify the optimal dose, long-term safety, and most importantly, the impact on liver histology and clinical outcomes. The Sherlock's Diseases of the Liver and Biliary System reference provides extensive detail on the complexities of MASLD and its management, underscoring the need for robust evidence.1

> **CLINICAL IMPLICATIONS**
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> Chiglitazar's Phase II data offer a glimmer of hope for MASLD patients burdened by hypertriglyceridemia and insulin resistance, a common and challenging subgroup. The significant reduction in liver fat and improvements in HOMA-IR are clinically meaningful, addressing core pathophysiological drivers of the disease. But this is a Phase II trial; the enthusiasm must be tempered by the need for larger, longer studies with histological endpoints.
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> Clinicians should note the peripheral edema and weight gain, which are not insignificant in a population already at high cardiovascular risk. Managing these side effects will be crucial if chiglitazar progresses to market. The pan-PPAR agonism is a double-edged sword, offering broad metabolic benefits but also carrying a known class effect profile that requires careful patient selection and monitoring.
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> The field desperately needs effective therapies for MASLD and MASH. While lifestyle interventions remain foundational, pharmacological agents that can reverse liver pathology are the ultimate goal. Chiglitazar's ability to tackle multiple metabolic derangements simultaneously positions it as a candidate worth watching, but its true place in the treatment algorithm awaits definitive Phase III data. Until then, it remains an investigational therapy.

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REFERENCES

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