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Commentary

Obeticholic Acid (OCA): Benefits and Challenges in NASH Management

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DESCRIPTION

Obeticholic Acid (OCA) is a synthetic bile acid that acts as an agonist of the Farnesoid X Receptor (FXR), a nuclear receptor that regulates bile acid synthesis, metabolism, and transport. OCA has been approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of Primary Biliary Cholangitis (PBC), a chronic autoimmune liver disease characterized by progressive destruction of the bile ducts. OCA is also being investigated for its potential in the treatment of Non-Alcoholic Steatohepatitis (NASH), a common and serious form of fatty liver disease that can lead to cirrhosis and liver cancer. NASH is a condition in which excess fat accumulation in the liver causes inflammation and fibrosis, resulting in impaired liver function and increased risk of complications. NASH is associated with obesity, diabetes, insulin resistance, and dyslipidemia, and affects up to 25% of the adult population worldwide. There is currently no approved pharmacological therapy for NASH, and the standard of care is lifestyle modification, such as weight loss, exercise, and dietary changes. OCA has been shown to improve the histological features of NASH in several clinical trials.

The FLINT trial, a phase 2 study, enrolled 283 patients with biopsy-proven NASH and randomized them to receive either OCA 25 mg or placebo once daily for 72 weeks. The primary endpoint was the improvement in liver histology, defined as a decrease in the NAFLD activity score (NAS) of at least 2 points without worsening of fibrosis. The trial was stopped early after an interim analysis showed that OCA met the primary endpoint, with 45% of OCA-treated patients achieving histological improvement compared to 21% of placebo-treated patients ($p<0.0001$). OCA also reduced fibrosis by at least one stage in 35% of patients compared to 19% of patients on placebo ($p=0.004$). However, OCA also increased the levels of Low-Density Lipoprotein Cholesterol (LDL-C) and decreased the levels of High-Density Lipoprotein Cholesterol (HDL-C) in the OCA group compared to the placebo group. The REGENERATE trial, a phase 3 study, enrolled 1968 patients with biopsy-proven NASH and fibrosis stage F2 or F3, or F1 with at least one accompanying comorbidity, and randomized them to receive either OCA 10 mg, OCA 25 mg, or placebo once daily for 18 months. The primary endpoints were the improvement in liver fibrosis by at least one stage without worsening of NASH, and the resolution of NASH without worsening of fibrosis. The trial reported the results of a planned interim analysis after 18 months of treatment. OCA 25 mg met the primary endpoint of fibrosis improvement, with 23.1% of patients achieving this outcome compared to 11.9% of patients on placebo ($p=0.0002$). OCA 10 mg did not meet this endpoint, with 17.6% of patients showing fibrosis improvement compared to placebo ($p=0.18$).

CONCLUSION

Neither dose of OCA met the primary endpoint of NASH resolution, with 11.7% and 12.0% of patients on OCA 10 mg and 25 mg, respectively, achieving this outcome compared to 8.0% of patients on placebo ($p=0.18$ and $p=0.13$, respectively). OCA also increased the levels of LDL-C and decreased the levels of HDL-C in both OCA groups compared to the placebo group. The most common adverse effect of OCA is pruritus, or itching, which occurs in up to 50% of patients and can be severe and intolerable in some cases. Pruritus is dose-dependent and can be managed by dose reduction, interruption, or discontinuation of OCA, or by the use of antihistamines or bile acid. Other adverse effects of OCA include fatigue, headache, abdominal pain, nausea, diarrhea, and constipation. OCA can also cause liver injury in some patients, especially those with advanced cirrhosis, and should be used with caution and close monitoring in this population.

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