1st GLOBAL LIVER HEALTH FORUM

Therapeutic approaches for NAFLD

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Flash for webinar (~20 mins)

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Therapeutic approaches for NAFLD

Is it NAFLD or NASH?

Simple steatosis accounts for 80–90% of NAFLD cases, whereas NASH accounts for the remaining 10–20%.[1] In NASH, steatosis is accompanied by lobular inflammation, hepatocellular ballooning and variable degrees of fibrosis.[1] The accumulation of fat in the liver is associated with metabolic syndrome.[2] There is a large heterogeneity amongst patient phenotypes and the progression of liver disease.[3] A poor diet, high in refined sugar and saturated fats, is the major cause of NAFLD.[4]

Lifestyle modifications to reduce BMI

National and international guidelines provide advice on lifestyle modifications.[5] Key dietary recommendations for overweight/obese patients include decreasing caloric intake by 30% in relation to overall energy demand.[6] Patients should be advised to reduce their intake of saturated fats and trans fatty acids, sugar-containing drinks, and alcohol.[7] Following a Mediterranean style diet low in carbohydrates has been shown to be more effective than low fat diets in reducing steatosis.[8] Furthermore, regular physical exercise has been shown in a systematic review of 8 RCTs conducted in NAFLD patients ≥18 years to mobilize fat from the liver.[9]

There is a clear relationship between the magnitude of BMI reduction and improvement in liver histology. BMI reduction by 5% results in a significant decrease in the fat content of the liver.[10]

Bariatric surgery has been proven to be effective in patients with morbid obesity and NASH, with resolution of NASH in 85% of cases (94% with mild and 70% with severe form), and improvement in fibrosis in 33.8% of patients.[11] Laparoscopic sleeve gastrectomy has also shown potential as a treatment for NASH.[12]

Treatment of comorbidities

NAFLD/NASH treatment should involve therapy for all comorbidities, e.g. with metformin for T2DM, ARB or ACEI for HT and statins for dyslipidemia.[13]

Liver-directed therapies

The AASLD recommends that pharmacological liver-directed treatment be considered only in patients with histologically confirmed NASH ± hepatic fibrosis, but does not specify any drug.[6] Other guidelines, similarly, offer no clear direction for pharmacological intervention.[5,14–16] Some support for the use of pioglitazone and vitamin E in NASH is evident.[5]

ARB: angiotensin receptor blockers; **ACEi:** angiotensin-converting enzyme (ACE) inhibitors; **EPL:** essential phospholipids; **HT:** hypertension; **NAFLD:** non-alcoholic fatty liver disease; **NASH:** non-alcoholic steatohepatitis; **T2DM:** type 2 diabetes; **RCT:** randomized controlled trial;. **PPC:** Phosphatidylcholine; **UDCA:** Ursodeoxycholic acid.

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Is there a room for hepatoprotective drugs?

Professor Hartleb considers that hepatoprotective agents such as PPC, UDCA, and silymarin have value as treatments adjunctive to lifestyle modifications in NAFLD. Agents such as these are not typically mentioned in international guidelines, however, in national recommendations hepatoprotectants are considered in different perspectives. In Polish guidance statements, hepatoprotectants, including PPC, are considered as adjunct therapy in patients with low-risk NAFLD.[16]

The use of EPLs in NAFLD/NASH have been evaluated in RCTs and observational studies.[17] Recently, a large real-world study evaluated adjunctive EPL treatment.[18]

Drugs under investigation in phase 3 trials

Five drugs are currently in active phase 3 trials for the treatment of NASH: Obeticholic acid, Cenicriviroc, Elafibranor, Resmetirom and Aramchol.[19–23]

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Learning objectives:

A healthy lifestyle is the cornerstone of NAFLD prevention and management.

Awareness of comorbidities (obesity, diabetes, arterial hypertension, dyslipidemia) is essential to NAFLD management.

Hepatoprotective medications have varying roles in NAFLD.

The correct choice of liver-directed therapy is important in biopsy-proven NASH.

Innovative therapies are being explored in clinical trials.

Main take aways:

- NAFLD is a systemic disease, all comorbidities need to be managed.
- In non-NASH, dietary restrictions and physical activity are usually the exclusive mode of treatment.
- In NASH ± fibrosis, liver-directed therapies are needed, but recommendation is difficult because of insufficient evidence of efficacy or unfavorable safety profile.
- Emergence of an efficacious drug would lead to a surge of NAFLD diagnoses, with a concurrent increase in referrals of patients with advanced fibrosis.

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