Combination treatment in MASLD – the next frontier

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Metabolic dysfunction associated steatotic liver disease (MASLD), previously known as NAFLD, is the most prevalent chronic liver disease in western countries and a growing cause of liver-related morbidity and mortality. Until very recently, there was no approved treatment for MASLD other than lifestyle interventions and management of the metabolic comorbidities. This has recently changed, with the conditional approval of resmetirom in the US for patients with steatohepatitis and at least significant liver fibrosis[1]. However, resmetiron is not approved outside the US, and still needs to demonstrate that it can reduce clinical outcomes in order to get full regulatory approval.

MASLD has a multifactorial pathogenesis and as such distinct factors might influence disease progression in different individuals[2]. This might in part explain the relatively modest therapeutic effect of investigational medicinal products and the several failures that have been recorded so far in clinical trials[3]. Potential therapeutic targets include metabolic processes in the liver or the adipose tissue, inflammation, apoptosis, fibrosis or gene therapy (silencing gain of

function variants or silence genes that encode loss of function variants)[4]. Given the potential co-existence of diverse factors driving disease progression in the same patient, combination treatment is the next logical step in drug development to maximise treatment efficiency. The mechanism of action of combined drugs should be such that ideally a synergistic action is achieved.

Weight loss is associated with improvement in histological features in MASLD, with a 7% decrease of total body weight associated with resolution of steatohepatitis and a 10% decrease associated with improvement in fibrosis[5]. Data from bariatric surgery series suggest that resolution of steatohepatitis is fairly quick and can happen within 12 to 18 months, while improvement of fibrosis takes longer[6]. GLP1 agonists induce weight loss and are increasingly used for the treatment of type II diabetes or for the medical management of obesity. Phase II data in NASH with significant or advanced fibrosis suggested that semaglutide is potentially beneficial in such patients[7] and a phase III trial is ongoing (NCT04822181) with results from the interim analysis expected in 2025. Efruxifermin is an FGF21 analogue

in injectable form that has shown positive results in both phase IIa and phase IIb trials[8, 9].

In this issue of CGH, Harrison and colleagues presented data from a prespecified analysis of a dedicated cohort with MASH and taking a GLP-1 receptor agonist for at least 3 months[10] from the phase IIa efruxifermin trial[8]. The primary objective of this prespecified analysis was to evaluate the safety and tolerability of efruxifermin when added to a GLP-1 receptor agonist. The authors reported data from 31 patients, of who 21 were taking efruxifermin and 10 were taking placebo. In terms of GLP-1 receptor agonists, 48% were taking semaglutide, 45% were taking dulaglutide and 7% were taking liraglutide. Safety and tolerability were comparable between the efruxifermin and placebo groups, suggesting that a combination treatment of efruxifermin and a GLP-1 receptor agonist has an acceptable side effect profile. Importantly, the addition of efruxifermin resulted in a significant reduction in the hepatic fact fraction, with normalization in 88% of this group compared to 10% in the placebo group. There were also significant reductions in non-

invasive fibrosis markers including the ELF score and liver stiffness values, transaminase levels, insulin sensitivity, HBA1c and lipid levels. It should be underlined that more than half of patients were taking dulaglutide or liraglutide, which are not as potent in terms of weight loss compared to semaglutide. Moreover, the indication of semaglutide was type II diabetes rather than obesity, therefore the dose was relatively low.

This small cohort provides proof-of-concept data on the safety and efficacy of combination treatments in MASLD. Similar efforts in combination trials were hampered by the lack of efficacy of the drugs used[11, 12]. Given the increasing prevalence of obesity and diabetes, it is projected that GLP-1 agonists will be the backbone of treatment in an increasing number of patients with metabolic comorbidities, including MASLD. Indicatively, 14% of patients enrolled in the resmetirom phase III trial were taking a GLP-1 agonist[1]. Should GLP-1 agonists also get conditional approval for at risk MASH, these numbers will increase further. The idea therefore of their combination with other approved treatments is the next logical step

in the quest to benefit people with at risk MASH. Clinical trials of combination treatment are expected in the near future and will be the next frontier in MASH. The safety of the combination and the synergistic effect of the combined drugs will be key in translating these into clinical practice.

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