Aldafermin in non-alcoholic steatohepatitis (NASH): a cautionary tale for trial design

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Non-alcoholic fatty liver disease (NAFLD) is the most prevalent liver disease world-wide with increasing burden in terms of morbidity, mortality and healthcare costs[1]. As there are still no approved pharmacological treatments, NAFLD represents an area of unmet clinical need, with the potential of conditional regulatory approval of investigational medicinal products based on improvement of surrogate endpoints. There are several drugs in phase II and III trials and the expectation is that there will be licensed treatments in the next 2-5 years.

In this issue, Harrison and co-authors report the results of a phase IIb double-blind randomized controlled trial of once daily subcutaneous aldafermin versus placebo in patients with biopsy proven non-alcoholic steatohepatitis (NASH)[2]. Aldafermin is an engineered analogue of the human gut hormone fibroblast growth factor 19 (FGF19), which inhibits the de novo synthesis of bile ducts and improves energy homeostasis. In total, 171 patients were randomised 1:1:1:1 to receive aldafermin (0.3, 1 or 3 mg) or placebo for 24 weeks. The study did not meet the primary endpoint, which

was a 1-point improvement of liver fibrosis with worsening of NASH at 6 months. There were significant dose dependent improvements in several secondary outcomes, such as serum markers of liver fibrosis, liver blood tests, histological resolution of NASH and liver fat content as assessed by MRI-PDFF. The most common side effect was diarrhoea, which was significantly more prevalent in the 3 mg aldafermin dose compared to placebo.

There are several points that are worth discussing. Although the primary endpoint was not met, it is likely that this was due to a combination of the power calculation and the short study duration, leading to an underpowered study. The key assumption was that 50% of the patients in the study group would reach the primary endpoint in the aldafermin group compared to 15% in the placebo group. This calculation was based on a 42% improvement of liver fibrosis by one stage in a single arm 12-week study of 19 patients with NASH on 3 mg of aldafermin[3] and of a 38% improvement in a 24-week randomized trial of 53 patients on 1 mg of aldafermin[4]. The authors also used the Multiple Comparison Procedure – Modelling

(MCP-Mod) method, which allows the detection of a dose response and slightly smaller sample sizes. Therefore, the assumed treatment effect was inflated by 8-12% compared to previous documented efficacy, whereas the placebo effect was relatively low compared to the published literature [5]. Moreover, a study duration of 6 months is most likely inadequate to show improvements in fibrosis using a semi-quantitative 5-stage histological score. Regulatory authorities recommend a 12-18 month duration of phase II trials with histological endpoints[6]. Development of fibrosis in NASH is multi-factorial and it takes years for patients to progress to a 1-point higher stage. Indicatively, studies of patients who achieved significant weight loss through bariatric surgery showed a 33.8% improvement of fibrosis at 12 months[7]. An additional consideration is that the progression or regression of fibrosis in the semi-quantitative scale is not linear – regression from stage 3 to stage 2 is not similar to regression from stage 2 to stage 1. A morphometric assessment of fibrosis through measurement of the collagen proportionate area or

an artificial intelligence approach could have provided more subtle indications of improvement in fibrosis[8].

The second point worth discussing is that there was no improvement in metabolic parameters such as weight or glycaemic control. Moreover, there was a dose-dependent increase in LDL cholesterol, which was counteracted by a protocol of rosuvastatin administration. Indeed, 84% of patients on 3 mg of aldafermin were on a statin at 24 weeks of treatments as compared to 42% at baseline. This would be a potential concern if aldafermin obtains regulatory approval, in terms of long-term cardiovascular safety and/or suitability for patients at high risk for cardiovascular events who are already receiving high does statins for secondary (or primary) prevention of cardiovascular events.

In conclusion, this phase IIb trial was inconclusive and did not provide a clear signal for further development in a phase III. The relatively short study duration and the over-optimistic power calculation may have contributed to the negative findings. Ongoing assessment of the liver biopsies from this study using artificial intelligence and the

study of aldafermin in NASH cirrhosis (https://clinicaltrials.gov/ct2/show/NCT04210245) will hopefully provide more clear answers. In the meantime, the study design should serve as a cautionary tale to other drug developers in the field.

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