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Surrogate endpoints in clinical trials for non-alcoholic steatohepatitis: the need for quantitative fibrosis assessment

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We read with interest the viewpoint on the use of the "fibrosis benefit index" as a surrogate outcome in registration trials for non-alcoholic steatohepatitis (NASH)[1]. Effective NASH treatments are indeed an unmet clinical need; given the relative long natural history of NASH, validated surrogate endpoints are required. Primary endpoints in current phase IIb or III trials include the resolution of NASH without worsening of fibrosis or the improvement of fibrosis without resolution of NASH.

The resolution (or improvement) of NASH is a problematic endpoint, as it has unacceptably high inter- and intra-observer variability and more importantly has consistently failed to correlate with clinical outcomes[2]. Therefore, investigational medicinal products in trials that are using this endpoint are in peril of a "false positive" or "false negative" signal for further development or licensing.

The second surrogate endpoint, improvement in fibrosis, is assessed through a 5-point semi-quantitative scoring system that takes into account both architecture and fibrosis. Although each stage has an assigned number, there is no quantitative relation between stages, i.e. stage 2 doesn't mean twice as much fibrosis as stage 1[3]. Importantly, the progression (or regression) of fibrosis is not linear and varies depending on the severity of liver disease. The main issue is that progression or regression through stages might not be observed in the relative short duration of trials. The proposed benefit index accentuates this problem, as it requires either resolution of fibrosis or progression to cirrhosis. For patients with advanced fibrosis, resolution of fibrosis is a contentious issue, while for those with lesser stages progression to cirrhosis might take more than a decade.

The fibrosis benefit index will only improve the assessment of treatment outcome only if fibrosis is precisely assessed with an objective quantitative methodology. We therefore propose the use of quantitative fibrosis assessment using collagen proportionate area (CPA) as a surrogate endpoint and the abandoning of the steatohepatitis component. CPA is a pure measure of fibrosis, can sub-classify cirrhosis and correlates with both HVPG and clinical outcomes[4]. More importantly, we recently validated CPA in NASH; we showed that it reliably measures peri-cellular fibrosis in pre-cirrhotic NASH and is an independent predictor of clinical outcomes[5]. CPA has excellent inter- and intra-observer variability and is not time consuming. More importantly, it can capture meaningful changes in fibrosis in a shorter timeframe than progression through semi-quantitative stages and thus provide an accelerated pathway for drug development and registration.

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