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Ursodeoxycholic acid for primary biliary cirrhosis: lesson for the future?

To the Editor:

A 'rebuttal' of the results of a meta-analysis [1] and a systematic review [2] published in 1999 has appeared in an Editorial in *Journal of Hepatology* [3].

The two independently performed meta-analyses – one performed as a traditional meta-analysis [1] and one as a Cochrane Hepato–Biliary systematic review [2] based on a published protocol [4] – have demonstrated that there is no statistically significant evidence supporting that ursodeoxycholic acid (UDCA) beneficially affects the rate of mortality and/or liver transplantation in patients with primary biliary cirrhosis (PBC) compared to placebo/no intervention.

The Editorial on the subject [3] disregards the negative finding of the recently published Pares et al. trial [5] on the issue and claims that the results of the meta-analyses are biased. To this we have the following comments:

First, it has been demonstrated that the results obtained in individual patients data (IPD) meta-analyses are the same as in meta-analyses based on aggregate data from the same trials ([6] unpublished observations). IPD are not easily available, and therefore most IPD-meta-analyses will be based only on a fraction of the evidence. Consequently IPD-meta-analysis may be misleading because of trial selection bias. Thus IPD meta-analyses should call for a cautious conservative interpretation [7].

Second, the Editorial [3] presents a meta-analysis based on only five of the 16 trials that have been performed [2]. This may imply a marked trial selection bias and thus be highly misleading [7].

Third, it is not surprising that different quality scores lead to different quality assessment of randomised clinical trials [8]. However, in the Goulis et al. meta-analysis [1] as well as in the systematic review [2], including all identified trials on the issue, both the low quality trials and the high quality trials were unable to demonstrate any statistically significant effect of UDCA versus placebo/no intervention on PBC mortality. These analyses [1,2] are sufficiently strong to contradict the combined analyses using a biased selection of the evidence base as presented by Poupon et al. [9].

Fourth, the claim by the Editorial [3] that 'it is well established that meta-analysis is inferior to actual data obtained from larger trials' is not supported by the work of Le Lorier et al. [10], who found that agreement between meta-analyses and large clinical trials was fair.

We do not contest that UDCA affects certain biochemical tests, including serum bilirubin levels, and possibly liver histology of PBC patients [3]. However, these outcomes are weak surrogates for what the patients really want, i.e., improved survival and quality of life [11]. Therefore, we disagree [1,2] with the conclusion of the Editorial that UDCA affects mortality or the combined outcome measure of mortality and liver transplantation [3]. This lack of effect on mortality is supported by the recent findings of a long-term follow-up randomised trial [12]. We therefore also disagree with the recommendation [3] that future efforts should focus on improving the efficacy of UDCA. On the contrary, in our opinion, it is now time to focus the attention on development of more effective interventions in this disease, evaluated in large trials of high methodological quality.

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