To the Editor:

We read with interest the recent EASL Clinical Practice Guidelines on management of cholestatic liver disease [1]. We would like to congratulate the authors on the correct grading of evidence for the use of ursodeoxycholic acid (UDCA) in patients with primary biliary cirrhosis (PBC) but at the same time we would like to challenge them about the interpretation of data.

Levels of evidence are designed as objective tools based on widely accepted defined criteria. The authors correctly used a grade II-2/B1 recommendation for use of UDCA in PBC, as data to support this are only available from "cohort or case–control analytical studies". In contrast, the recent AASLD clinical practice guidelines [2] give a different level of evidence for use of UDCA, which is Class I, level A i.e. data to support this are “derived from multiple randomized clinical trials or meta-analyses”. This grading is methodologically incorrect and probably reflects opinion rather than evidence. In fact, no single randomized controlled trial to date has demonstrated a significant effect of UDCA in terms of survival or liver transplantation, and neither have a meta-analysis nor a Cochrane review, which evaluated all randomized trials [3,4].

Although the authors of the EASL guidelines criticize the published meta-analyses [3,4] for including studies with short duration or with use of inadequate doses of UDCA, this criticism is not justified. The Cochrane review with updated and longer follow-up data still failed to find benefit of UDCA [3], and sensitivity analyses regarding UDCA dose in both meta-analyses showed no difference between standard doses (>13 mg/kg) versus lower doses with respect to major outcome measures [3,4]. Even a selective analysis of raw data from the French, Canadian and Mayo cohorts showed a possible benefit of UDCA only in patients with moderate and severe disease [5], in whom currently even those clinicians who feel UDCA is effective, acknowledge that it is less likely to exert a beneficial therapeutic effect.

As regards the interpretation of evidence, the crucial issue is the fact that in those studies in which cross-over from placebo or no treatment to UDCA occurred, (after approximately 2 years) the cross-over patients deteriorated despite using UDCA [4]. A potential solution to evaluate this paradox was given in correspondence from us [6]. Nevertheless, our suggestions for analysis have never been taken up. However, we acknowledge that in early stage and/or asymptomatic PBC, UDCA may have benefit – but conclusive evidence is lacking. Data to support the use of UDCA in early asymptomatic PBC needs strengthening. Indeed, the “Paris” and “Barcelona” criteria mentioned by the authors, refer to cohorts with no

Ursodeoxycholic acid and primary biliary cirrhosis: EASL and AASLD guidelines

Gary J. Cowin
Centre for Magnetic Resonance, The University of Queensland, German Sciences Building, St. Lucia, Brisbane 4072, Australia
Tel.: +61 07 33658378; fax: +61 07 33653833.
E-mail address: gary.cowin@cmr.uq.edu.au (G.J. Cowin)

Julie R. Jonsson
School of Medicine, Southern Clinical Division, The University of Queensland, Brisbane, Australia

Stuart McPherson
School of Medicine, Southern Clinical Division, The University of Queensland, Brisbane, Australia


control groups and thus data interpretation should be made with great caution [1]. In the asymptomatic PBC cohort described by Prince et al. (only 7% of patients were taking UDCA), 45% did not develop a liver-related symptom during a median follow-up of 7.4 years [7]. These could be the same patients who “respond” to UDCA.

Moreover, the emphasis in the guidelines for evidence of histological improvement is misplaced, as we have previously pointed out [8]. Notably, in the original trials there were patients in the non-fibrotic stages of PBC progressing to fibrosis, despite an improvement in inflammation [3,4]. This dichotomy between improvement in inflammation but worsening of fibrosis is difficult to interpret as an improvement in histological stage.

In conclusion, the absence of best-level evidence confirms that UDCA for all PBC patients remains an unresolved issue. Currently, the highest level of evidence (meta-analysis of randomized trials) suggests that UDCA does not influence patients’ survival, time to transplantation, or any other patient-important clinical outcome [3,4].

References

Ursodeoxycholic acid in primary biliary cirrhosis: Reply

To the Editor:

We thank Dr. Tsoschatzis et al. for their comments. In the EASL Clinical Practice Guidelines (CPG), we discussed in detail relevant data available to provide a balanced discussion of the pro’s and con’s of ursodeoxycholic acid (UDCA) treatment in primary biliary cirrhosis (PBC) [1]. Tsoschatzis et al. address the difficulty of finding a long-term benefit of medical treatment particularly in patients in the early stages of a slowly progressive disease which usually has a course of up to two decades [1,2]. We agree with the authors that additional data on the use of UDCA in asymptomatic, early-stage PBC would be most welcome to further support the beneficial long-term effect of UDCA in early PBC. In clinical practice, however, it appears impossible (in light of the data currently available) to perform high-quality randomized, placebo-controlled trials over a period of one to two decades in a cohort of well-informed early-stage patients large enough to demonstrate a clear-cut survival benefit also in this subgroup. Therefore, the data presented from the most recent studies of cohorts followed for a period of at least a decade [3–5] appeared of value to us when we recommended medical treatment of early-stage disease with UDCA [1].

A careful analysis of the available data deriving from randomized controlled trials of high-quality suggest that also in early-stage PBC, UDCA led not only to improvement of biochemical markers including surrogate markers of survival, but also halted progression of histological stage. The Spanish randomized, placebo-controlled multicenter trial was the first large high-quality study which addressed this issue by including only patients with stage 1–3 disease [6] and carefully following them over a median period of 3.4 years to guarantee adequate compliance (a factor which often receives inadequate attention and deserves consideration when discussing the dichotomy of short-term improvement of biochemical markers and inflammation, but worsening.