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


Emmanuel A. Tsocatzis
The Royal Free Sheila Sherlock Liver Centre and Division of Surgery, Royal Free Hospital, London, UK

Kurinchi S. Gurusamy
Department of Surgery, UCL Medical School, Royal Free Campus, London, UK

Christian Gluud
Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark

Andrew K. Burroughs
The Royal Free Sheila Sherlock Liver Centre and Division of Surgery, Royal Free Hospital, Pond Street, Hampstead, London NW3 2QG, UK

E-mail address: andrew.burroughs@royalfree.nhs.uk
doi:10.1016/j.jhep.2009.09.018

Ursodeoxycholic acid in primary biliary cirrhosis: Reply

To the Editor:

We thank Dr. Tsocatzis 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]. Tsocatzis 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...
of fibrosis). Interestingly, in this carefully followed Spanish cohort, histological progression was clearly halted by UDCA treatment in comparison to placebo [6].

In contrast to this high-quality randomized, placebo-controlled trial, meta-analyses which include trials with a duration of up to two years for a disease with an estimated duration of up to two decades may be suited to analyze short-term biochemical effects of medical treatment, but certainly carry the risk of diluting the information needed for a well-based long-term survival analysis. The attempts of others [7,8] to provide meta-analyses which included long-term randomized, placebo-controlled trials for survival analysis only to avoid this dilution effect may deserve mentioning here; these authors [7] concluded that long-term treatment with mid-dose UDCA can improve liver biochemistry, delay histological progression in early-stage disease and improve survival-free of liver transplantation. We have to keep in mind that meta-analyses are only as good as the trials they include and have to be judged with some caution [9].

References


Ulrich Beuers
Department of Gastroenterology and Hepatology, Academic Medical Center, University of Amsterdam, P.O. Box 22700, 1105 AZ, Amsterdam, The Netherlands
Tel.: +31 20 5662422; fax: +31 20 6917033.
E-mail address: u.h.beuers@amc.uva.nl

Michael Trauner
Division of Gastroenterology and Hepatology, Department of Internal Medicine, Medical University of Graz, Graz, Austria

doi:10.1016/j.jhep.2009.09.018

Oral antiviral therapies are cost-effective vs. no treatment but indirect comparisons should be avoided

To the Editor:

In their recent paper Buti and colleagues [1] claim to have performed a “cost-effectiveness analysis of different oral antiviral therapies in patients with chronic hepatitis B”, but they did so presenting credible results in an inappropriate and potentially misleading manner.

By definition incremental cost-effectiveness ratio relates to incremental effectivenss put in relation to incremental cost. Therefore, the natural referent alternative for “oral antiviral therapies” is a therapy in which no antiviral therapy is used, what Buti and colleagues refer to as “no treatment”. Indeed Buti and colleagues [1] conceptually appraised decremental, rather than incremental, cost-effectiveness ratio, by unconventionally taking as a reference the point estimate “most efficacious treatment”. This is not a standard procedure in cost-effectiveness analyses. Consequently, the study would be much more informative presenting the incremental cost of (each) antiviral therapy compared to “no treatment” in relation to its incremental effectiveness. This is the standard approach widely adopted by public health technology assessment agencies. This approach has several advantages: (1) it informs decision makers on ICER (Incremental Cost-Effectiveness Ratio) of the various technologies, individually, that can be used compared to no treatment; (2) it does not require the use of a sophisticated model that would be needed to detect a meaningful and significant difference between active treatments; (3) it does not require problematic and sophisticated adjustments for differential characteristics of patients included in RCT’s (Randomized Clinical Trial) of different active treatments (e.g. different baseline viral load, differences in tolerability profile), which are required when (indirect) comparisons between active treatments are made. A careful reading of the paper by Buti and colleagues [1] confirms that the model seems to make accurate and discriminating predictions of costs and outcomes when “no treatment” on one side and