Response to the letter by Ooi et al.

Dear Sir,

We read with interest the letter from Dr. CY Ooi and Coll.[1] pointing out that more clinical and experimental evidence is needed before firm recommendations concerning long-term use of UDCA in CFLD are issued.

We agree that achieving substantial improvement, and even normalization, of liver biochemistries in CFLD patients while on UDCA treatment does not necessarily mean that administration of this bile acid is effective on clinical grounds. We also agree that there are few randomized trials that have addressed the potential efficacy and safety of UDCA in CFLD [2,3]. We have for many years discussed the need for prospective double-blind studies of UDCA treatment in patients with CF, but it has been difficult to get acceptance for these studies to date. On the other hand, evidence has been provided of stabilization in progression of CFLD while on UDCA, using liver biopsy, ultrasound and clinical symptoms as the outcome [4–7]. With regard to the dose, a dose–response study has clearly shown that in CF patients a biliary enrichment with UDCA comparable to that achieved in adults with both normal and abnormal hepatic function was only obtained at the dose of 20 mg/kg/day, that was also associated with greater biochemical improvement [8].

The concern expressed by Ooi et al. [1] about the use of UDCA in the treatment of patients with suspected CFLD is mainly based on the study of Lindor et al. [9] on its use in Primary Sclerosis Cholangitis (PSC), and on the fact that UDCA was not effective in very severe CFLD. Currently, it is not known why 2–5% of patients with CF develop severe liver disease and therefore it is not possible to identify those patients who would benefit. Practical experience and a single center study (published in abstract form) [10] indicate that UDCA is more beneficial when it is started before the onset of severe disease. It is not pertinent to compare CFLD with PSC as the diseases are different in etiology, pathology, degree of cholestasis and prognosis [11–13]. Furthermore, as pointed out by Lindor et al. [6], the authors used much higher doses than given in earlier studies in PSC with favorable results. It is well known that UDCA can be epimerized to chenodeoxycholic acid and also transformed by the bacterial flora to lithocholic acid [14], which both are liver toxic. It is likely that higher doses increase the risk of such transformation and as Lindor et al. did not investigate the bile acid pattern during long-term treatment, it cannot be excluded that this contributed to their negative results.

At present UDCA has been in clinical use since more than two decades and to the best of our knowledge no studies have shown clinically relevant adverse outcomes nor any unfavorable effects on liver disease progression that could be related to UDCA or to the doses recommended for CF patients.

We thank Dr. CY Ooi and Coll. for their comments, and appreciate their cautious approach suggesting a watchful eye to be always kept on CF patients undergoing UDCA treatment. Should sound data from any authors involved in CF patients’ management provide evidence of unfavorable effects to UDCA administration in long-term clinical studies or well documented clinical case reports, the present guidelines are ready for being promptly modified.

For our part, using mass spectrometry with stable-isotope dilution analysis, some of us are presently addressing the issue of possible UDCA toxicity in a clinical study exploring the metabolic fate of this bile acid in CF patients.

Meanwhile, we deem there are no compelling arguments for precluding CF patients to start UDCA early, before the liver disease has potentially progressed to a stage at which changing its course by any medical treatment is no longer possible.

References


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