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Oral Cholic Acid in Zellweger Spectrum Disorders: A Word of Caution

To the Editor: We read with interest the article by Heubi et al (1), which describes the use of cholic acid (CA) in patients with bile acid synthesis disorders due to a single enzyme deficiency and Zellweger spectrum disorder (ZSD). We believe that the design and presentation of the data importantly affect the interpretation of the authors on the reported effect and safety of CA, particularly in patients with ZSD. First, single enzyme deficiencies and ZSDs are 2 distinct disorders, and we strongly feel that results in patients with ZSD should be reported separately. The choice of a worst-to-best analysis (comparing the least favorable outcome before intervention with the best favorable outcome after intervention) is to the best of our knowledge an unacceptable statistical method in biomedical studies. We have found no references that validate its use in biomedical research. Type I statistical errors, detecting an effect that is not present, are likely to occur, particularly in the patients with ZSD who have a great natural variability of biochemical markers.

Our suggestion of a type I error is supported by a lack of significant effect of CA in patients with ZSD on all primary outcomes in the sensitivity analysis presented in the supplementary material. Another unaddressed aspect is the well-known phenomenon in ZSD of biochemical normalization in patients without intervention (2), a bias which cannot be ruled out since the interval of measurements is not specified.

The conclusion that CA is safe and well tolerated in patients with ZSD is in our view insufficiently supported by the provided data, as data on safety were registered in a nonstructured fashion and retrospectively. In a previous study, not discussed by Heubi et al (1), we systematically studied the effect of CA for 9 months in a well-defined cohort of 19 patients with ZSD (3). Although CA resulted in lower C₂₇-bile acid intermediates in plasma and urine, no clinical benefit could be observed. Rather, CA could even be harmful in patients with cirrhosis (3).

In conclusion, the beneficial effects of CA in ZSD still remain to be proven, while caution is required when initiating this treatment, particularly in those with advanced liver disease.

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Oral Cholic Acid Is Efficacious and Well Tolerated in Patients With Bile Acid Synthesis and Zellweger Spectrum Disorders

We would like to thank Klouwer and associates for their thoughtful comments regarding our recently published article, “Oral Cholic Acid is Efficacious and Well Tolerated in Patients with Bile Acid Synthesis and Zellweger Spectrum Disorders,” and would like to clarify a few of the points they raised (1). Although we agree that patients with single enzyme defects (SEDs) and Zellweger spectrum disorder (ZSD) represent 2 distinct and different classes of patients, our findings aim to provide a summary of the clinical information gathered that culminated in the approval of cholic acid (CA) by the Food and Drug Administration (FDA) in March 2015. The information reported included all patients who had been treated before approval of the new drug application. This includes a group of ZSD patients whose initial cohort was studied under an FDA Orphan Drug Grant (2) and subsequently individual patients who were enrolled with a final cohort of 20 ZSD patients included in the intent-to-treat analysis of CA. We do present the outcomes of urinary bile acid excretion, liver chemistries, and height/weight separately for the ZSD and SED cohorts in Figures 1–3.

The choice of the worst-to-best comparison was chosen because of the nature of the data, the rarity of the disease, and was based upon agreement between the sponsors and the FDA during the drug review process. The worst to best analysis provides patients and caregivers with information as to what type of efficacy they may be able to anticipate. This is critical as the natural history of ZSD is not well understood and our data provide important long-term insights into the clinical outcomes with CA treatment. Because this was not a randomized trial, participants did not have regularly scheduled study visits and were followed at a variety of sites throughout the United States and Canada. One of the goals was to determine the greatest potential impact that CA would have. As a consequence we utilized the worst baseline to the best post-treatment values. In addition, we added sensitivity analysis of best-to-best, worst-to-worst, and median to median; however, to best illustrate the true potential efficacy of the drug, we felt that the worst-to-best analysis was the best method available.

Our experience with CA treatment in 20 ZSD patients provides insight into long-term outcomes that may be anticipated with treatment of CA and varies from that of published experience of Berendse et al (3). Our findings report long-term outcomes of treated patients over a span of 18 years, whereas those of Berendse et al reported on 9 months of treatment. With 9 months of treatment, the Berendse study describes their group 1 patients as responding well to CA treatment, with a significant decline in C₂₇-bile acid intermediate levels in plasma and urine, and our review of Fig. 2 suggests liver function stabilized and was maintained during the study period in these patients. The authors