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The Effect of a Probiotic on Hepatic Steatosis

Steven F. Solga, MD^{*}, Gillian Buckley, MPH[†], Jeanne M. Clark, MD, MPH^{*,‡}, Alena Horska, PhD[§], and Anna Mae Diehl, MD^{||}

^{*}Department of Medicine, Johns Hopkins University Durham, NC School, Baltimore, MD

[†]Department of International Health, Johns Hopkins University Durham, NC School, Baltimore, MD

[‡]Department of Epidemiology, Johns Hopkins University Durham, NC School, Baltimore, MD

[§]Russel H. Morgan Department of Radiology and Radiologic Science, Johns Hopkins University Durham, NC School, Baltimore, MD

^{||}Department of Medicine Duke University, NC School, Baltimore, MD

To the Editor

Nonalcoholic fatty liver disease (NAFLD) is a serious and chronic liver disorder. The pathogenesis of NAFLD is uncertain, but some research suggests a role for gut flora.¹ This reasoning provided rationale to evaluate whether gut flora therapy could treat NAFLD in experimental murine models and indeed, “probiotics” were found to improve liver enzymes and liver histology.² Further, at least 1 previous study³ has suggested a beneficial effect of VSL#3 on liver disease in humans, though this study did not include histology or quantitative liver fat measurement. We hypothesized that a probiotic compound could improve liver fat in humans.

We evaluated the effect of VSL#3 on 4 adult human subjects with NAFLD in an open label pilot trial. Subjects were screened and provided informed consent. They received 1 sachet of the probiotic compound daily for 4 months. The main outcome measure was liver fat as measured by proton magnetic resonance spectroscopy (¹H MRS). ¹H MRS precisely and noninvasively quantifies liver fat,⁴ and we and others have found excellent reproducibility and reliability using this technique.⁵ In addition, we measured monthly blood assays (including comprehensive metabolic panel, protime, glycosylated hemoglobin, tumor necrosis factor α , interleukins 6 and 1 β , and interferon γ), collected clinical data (including height, weight, body mass index, and medication use), and finally, detailed stool analyses. ¹H MRS for hepatic steatosis was performed at study entry, at the end of 4 months, and again at 7 months (after washout).

The protocol was approved by the Johns Hopkins University Institutional Review Board and posted on clinicaltrials.gov (NCT00099723). An investigational new drug (IND) permit was obtained to evaluate VSL#3 for hepatic steatosis from the United States Food and Drug Administration (US FDA).

The 4 subjects had complete data collection and reported excellent compliance with the probiotic compound. Their body weight ranged from 79 to 100 kg (mean: 93 kg), with body mass index (kg/m²) 27 to 33 (mean 30).

To our disappointment, all 4 subjects experienced a significant increase in liver fat at the end of 4 months, and 3 subjects met our definition of a “meaningful” change with a >3% increase. After washout, 3 of the 4 subjects experienced a decrease in liver fat, with values that were close to baseline. The subject whose liver fat remained elevated gained 6 kg in body weight during the study. There were no significant differences in any of the blood assays or clinical parameters. The probiotic was well tolerated and there were no reported adverse events.

Our hypothesis that probiotics would reduce hepatic steatosis in humans was not supported. Instead, the data indicate the opposite trend among the first 4 subjects. As recently reviewed,⁶ negative trials may occur in fatty liver disease for several reasons, including variability in end points, wrong dose, preparation or length of treatment, and underpowered number of subjects. Our study had multiple limitations, including the fact that we only evaluated 1 dose and preparation of the probiotic compound.

Certainly, however, our study’s most important limitation was the small number of study subjects. Ideally, more subjects would have been enrolled. However, because our study was performed under an IND from the US FDA, it was closely scrutinized and was costly. Relatively few published probiotic studies have been conducted with an IND. As we and others, including our Institutional Review Board, consider NAFLD to be a disease (as opposed to a wellness state), the FDA oversight became mandatory. Although this involvement had many positive aspects, from a practical standpoint, it led to added costs and delays. Thus, when the preliminary results of our first 4 subjects clearly failed to support our hypothesis, we elected to end the protocol.

It must be acknowledged that the component bacteria that make up VSL#3, like many probiotic compounds, can be difficult to identify and separate from other endogenous *Bifidobacterium*, *Lactobacillus*, and *Streptococcal* spp. Therefore, it can be challenging to make firm conclusions about how, if at all, a given probiotic affects the overall microbiota. Our dose, which was based on the dose of VSL#3 in other human studies, may simply have been inadequate for this indication. Human gut flora studies can be challenging because the science is relatively nascent.

Our hypothesis may simply be wrong. Pilot studies carried out in murine models have their own significant limitations and the results may not be applicable to humans.⁷ However, despite our results, we believe,⁸ along with many others,^{9–11} that there is sound scientific rationale supporting a role for gut flora therapy in liver disease. Further research is needed to determine the optimal formulation and dose of gut flora therapies.

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