Journal of Inherited Metabolic Disease (2018) 41:915
https://doi.org/10.1007/s10545-018-0249-1

LETTER TO THE EDITOR

Response letter

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Published online: 27 September 2018

Dear Editors,

We appreciate the comments and thoughts regarding gene therapy in the naturally occurring canine model of glycogen storage disease type Ia (GSD-Ia). We agree that nutritional therapy can prevent complications in humans with GSD-Ia (Dambska et al. 2017), but nutritional therapy by itself did not prevent complications in our dogs. It is, therefore, critical not to minimize the contribution from the gene therapy, especially since there is good evidence in the murine model that rAAV-mediated gene therapy can prevent hepatocellular adenoma/carcinoma (HCA/HCC) formation if adequate hepatic glucose-6-phosphatase-α (G6Pase-α) enzymatic activity was obtained (Lee et al. 2012; Kim et al. 2017).

There were several important factors which likely explain the differences between the trials. The first key difference between the two studies is the efficacy of the vectors used. A study independently conducted and jointly published by Duke and NIH researchers demonstrated that the efficacy of the NIH vector used by our group is at least 3.5-fold more effective than the vector used to treat the dogs at Duke University (Lee et al. 2013). A second key difference was the condition of the G6Pase activity assay, microsomal versus total lysate. The microsomal G6Pase enzymatic assay is the gold standard in the field. It is critical to note that the Duke group used total liver lysates for their G6Pase activity assay, and their background activity averaged ~ 14% of the control activity. In contrast, our group used microsomal G6Pase activity assay and our background activity was less than 1% of the control activity. A third key difference between the studies was the state of the liver at the time of the infusion. Hepatic transaminase elevation has been associated with loss of the transgene in gene therapy trials in animals and humans (Manno et al. 2006). Nutritional therapy prior to treatment resulted in markedly lower AST and ALT concentrations, and the extremely elevated values in the Duke cohort likely contributed to loss of the transgene.

The safety of gene therapy is paramount, and understanding the risks and benefits is critical, particularly since clinical trials for human GSD-Ia patients have commenced using AAV8 for gene transfer of G6Pase-α. As the human trials progress, it remains critical to monitor all GSD-Ia patients for long-term complications.

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