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a. Title of your presentation

CASE REPORT: Liver Failure in a 4-month-old male with SMA type 2 after gene therapy/Onasemnogene abeparvovec (Zolgensma)

b. Authors and Affiliations

Juliana Hager, MS3

c. Faculty Mentors

Dustin Paul, MD, Pediatric Neurologist

d. Introduction (Provide a brief literature review of the research topic).

Spinal muscular atrophy (SMA) is characterized by muscle weakness and atrophy resulting from progressive degeneration of the anterior horn cells in the spinal cord and the brain stem nuclei. The onset of weakness ranges from before birth to adulthood. The weakness is symmetric, proximal > distal, and progressive.

Onasemnogene abeparvovec (ZOLGENSMA) is a viral vector-based gene therapy designed to deliver a functional copy of the human survival motor neuron (SMN) gene to the motor neuron cells of patients with spinal muscular atrophy (SMA). It was approved in May 2019 in the USA for the treatment of pediatric patients aged < 2 years with SMA and bi-allelic mutations in the SMN1 gene. There has been significant motor function gain from the patients in and out of the clinical trials

However, it can cause an immune response that could lead to an increase in enzymes produced by the liver. In one paper that studies over 100 SMA patients treated with Onasemnogene abeparvovec, 34% had a least one adverse event within the hepatotoxicity category. All adverse events associated with increased serum aminotransferases concentrations resolved completely with the majority receiving prednisolone from 60–120 days.
Our case study bellow is of another SMA type 2 male, treated with Onasemnogene abeparvovec IV infusion therapy that presented 23 days later with liver failure.

e. Objective (Describe the purpose of the research project and place the objective in a larger context).
The purpose is to present an adverse reaction to the gene therapy/ZOLGENSMA given to a SMA 2 patient, there is not a lot of literature out there on adverse events to this drug that was recently approved in 2019 here is the case presentation:

4 month, 21 day old male with a past medical history of Spinal Muscular Atrophy (SMA) type two was administer an IV infusion of the gene therapy, Zolgensma. His diagnosis was achieved before he was symptomatic because of his older sisters diagnosis of SMA type II. After reviewing the diagnosis with mom and the benefits and risks to all of the three treatments that are approved by the FDA for SMA type 2 (onasemnogene, nusinersen, and risdiplam), the mother chose gene therapy, Zolgensma (onasemnogene). The patient was referred to occupational, physical, and speech therapy. He was also referred to a local pediatric cardiologist and a pediatric pulmonologist for disease related restrictive lung disease. Per the pulmonologist's recommendations, he was doing cough assist about 3-5 times per day and was also started on Synagis intramuscular for RSV prevention because of his neuromuscular disease process and inability to clear secretions.

Antibodies to the adeno-associated viral vector were measured in his serum before the treatment, his titer showed 1:25 which cleared him for treatment, anti-AAV9 antibody titer of <1:50. Twenty-four hours prior to the Zolgensma infusion, he received prednisone 1 mg/kg. After the infusion, he was admitted to the PICU for one day and was started on a prednisone taper for four weeks: week 1- 10 ml daily, week 2 - 9 ml daily, week 3-8 ml daily, week 4-7 ml daily. He was also getting weekly LFT's, CBC, and Troponin-I levels drawn for four weeks after infusion to observe for any symptoms of potential acute myocarditis and hepatitis side effects of the gene therapy.

Twenty two days after the infusion and following the prednisone taper, his labs showed elevated liver enzymes, troponin, and platelets.. His prednisone dose was increased to increase to 12 ml daily + Ranitidine and he was followed in the clinic a few days later. In the clinic, he is noted to have mild jaundice of the sclera and skin, and he was alert and active. As per mom, she noticed that he began having a yellow tint to the skin and of the eyes 26 days after the infusion. He had been eating well, however, she noticed that his stools are now more pale than previously. She also notes that he was sleeping more and has decreased activity levels. Stat labs were ordered to assess liver function including: ammonia, PT/PTT, INR, total/direct bilirubin, albumin, troponin, CMP, and CBC. He was found to have decreased liver function and admitted to the ICU.
(PATIENT IS STILL IN THE ICU- NEED TO UPDATE LAB VALUES next week)

f. Methods (Explain what you did in your research project. In this section consider using graphs, histograms, and other visuals to display your method).
This is a case report so I will just be explaining the history and physical findings and lab results

g. Results (Describe what was learned and provide outcomes for the main results. Relate the results to the objective. Be brief and include only the most important findings from your study and your interpretation of your data).

This is a case study on an adverse event to the gene therapy Zolgensma. My methods will include lab values, and the history and physical findings, MOA of the gene therapy, treatment of the liver failure that resulted from the gene therapy**.**
(PATIENT IS STILL IN THE ICU- NEED TO UPDATE LAB VALUES next week)

h. Discussion
Due to how rare SMA is and the novel new treatment of onasemnogene abeparvovec, a treatment protocol for the adverse reaction of liver failure has not been standardized**.**

i. Conclusions (Briefly identify significant findings and impact of work in the context of previous research. Describe study limitations, strengths, and how work will contribute to the field. Identifying 'next' steps or future directions that the research/scholarly/creative work might take).
Next steps include reporting the adverse effects of this treatment, continue gathering data on treated patients, and developing a standardized treatment for patients who develop severe liver failure to onasemnogene abeparvovec gene therapy.

j. Acknowledgements (If your project was funded (all or part) from grants and/or awards, identify the source(s) of support. You also can acknowledge individuals that provided data and/or feedback to you).
Not affiliated with any financial support. Dr. Dustin Paul is the pediatric neurologist that I worked closely beside and provided me the patient case and feedback

k. References
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