ePP034

Retrospective Study of the Disease Course in Pediatric Patients With Severe MMA Caused by *MMUT* Mutations

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Conclusions

- This retrospective study characterizes disease progression in pediatric patients with severe MMA associated with MMUT deficiency who were medically managed or were the recipients of a liver transplant
- All enrolled patients underwent newborn screening for MMA, and the majority received their initial diagnosis through this testing, reflecting the current treatment setting of widespread newborn screening
- Patients receiving liver transplants were 6 years or younger at the time of transplant; thus, the management they received reflects the evolving treatment paradigms for MMA, which emphasize liver transplant at increasingly younger ages
- Across all patients, length/height tended to be lower than normal throughout the study period while weight was mostly higher than normal, resulting in an elevated BMI
  - In patients who received a liver transplant, length/height stayed low, but weight and BMI increased significantly after liver transplant and then returned close to baseline levels
- Despite using MMA-related prescription medications, patients may continue to require emergency medical attention and may continue to exhibit elevated methylmalonic acid levels
  - In patients who received a liver transplant, there was a rapid and sustained decrease in methylmalonic acid levels and, while levels did not approach normalization, there was an apparent reduction in variability

Background

- Isolated methylmalonic acidemia (MMA) is an inherited metabolic disorder most commonly caused by a deficiency of the mitochondrial enzyme methylmalonyl-CoA mutase (MMUT), which blocks metabolism of methylmalonyl-CoA to succinyl-CoA[1,2]
- Patients who are asymptomatic at birth may be diagnosed through expanded newborn screening programs; patients with severe MMA may present in the neonatal period with a metabolic crisis, displaying signs including poor feeding, vomiting, hypotonia, hypothermia, respiratory distress, and progressive encephalopathy[1,3,4]
- In addition to intermittent, often life-threatening metabolic crises, patients with MMA are at risk of neurologic symptoms, failure to thrive, intellectual disability, severe infections, and progressive renal insufficiency[1,2]
- Currently, there are no curative therapies for MMA, although liver transplants are increasingly performed in patients with severe, early-onset disease to partially correct the enzymatic defect[3,5,6]
- Natural history studies that provide longitudinal data are needed to increase the understanding of disease progression and support interventional studies of genetically targeted therapies

Objective

- To characterize the disease course in the era of newborn screening for patients with severe MMA associated with MMUT deficiency among 2 cohorts: pediatric patients managed medically from birth to age 3 years (cohort 1) and pediatric-age recipients of liver transplant (cohort 2)

Methods

Study Design

- This was a retrospective natural history study that enrolled pediatric patients diagnosed with severe MMA by newborn screening, who were identified by participating investigators and/or appropriately delegated study staff
- Patients were assigned to cohort 1 and/or cohort 2 based on eligibility criteria

Study Population

Key inclusion criteria

- Diagnosis of severe, mutase-deficient MMA by newborn screening based on the following criteria:
  - Any patient with confirmed mut^0 genotype (null mutation)
  - Any patient with confirmed mut$^-$ genotype (partial deficiency) with a documented peak serum or plasma methylmalonic acid level of ≥100 µmol/L
- Medical records available to cover the following time periods:
  - Cohort 1: period from birth to the patient's third birthday (or earlier if deceased)
  - Cohort 2 (patients who have received a liver transplant, regardless of age at transplant):
    - » Diagnosis confirmation
    - » 1-year period before liver transplant (or less if transplant prior to first birthday)
    - » 1- to 3-year period after liver transplant (or earlier if deceased)
- Voluntary agreement from the patient (and/or parent[s] or legally authorized representative) to participate by giving written informed consent/assent in accordance with the good clinical practice guidelines of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use and with applicable local regulations, unless the associated institutional review board or ethics committee provides an appropriate consent waiver

Key exclusion criteria

- History of a clinically significant medical condition unrelated to MMA, in the opinion of the investigator
- Expectation that relevant medical records will not be available, in the opinion of the investigator
- Diagnosis of organic acidemias other than isolated MMA, or with any other causes of hyperammonemia
- Prior treatment with an MMA-targeted gene therapy or nucleic acid therapy
- Prior kidney transplant

Data Collection

- Upon signing of the consent/assent and confirmation of subject eligibility via evaluation of the inclusion/exclusion criteria, deidentified patient data were entered into a confidential patient information (electronic) database
- A set of core elements related to the patient's diagnosis, growth and developmental parameters, dietary management, medications, healthcare utilization, and key laboratory parameters were collected from medical record review

Statistical Methods

- Statistical analyses were primarily descriptive in nature, except for comparison of pre- and posttransplant data for cohort 2, when a Wilcoxon matched-pair signed rank test was used
- Baseline is the first nonmissing result prior to 1 month post birth for cohort 1 and the last nonmissing result prior to the liver transplant for cohort 2

Results

Study Population

- A total of 18 patients were enrolled in the study
  - One patient from cohort 2 died due to cardiac arrest during liver transplant
- Demographics, disease characteristics, and medical management during the defined study periods for cohorts 1 and 2 are summarized in **Table 1**

Table 1. Demographics, Disease Characteristics, and Medical Management During the Study Period

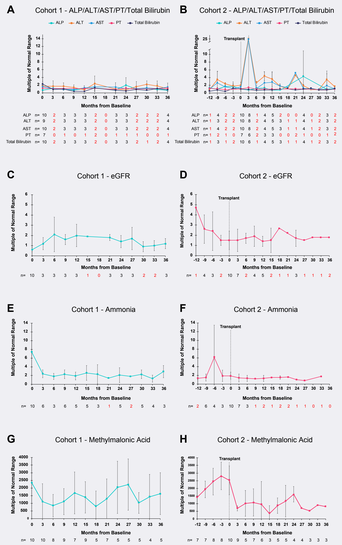
	Cohort 1 (n=10)	Cohort 2 (n=10)
Age at diagnosis, days		
Mean (SD)	7.5 (6.5)	5.7 (2.6)
Range	1-23	2-10
Sex, n (%)		
Male	5 (50.0)	4 (40.0)
Female	5 (50.0)	6 (60.0)
Initial method of diagnosis, n (%)		
Newborn screening	8 (80.0)	7 (70.0)
Crisis[a]	2 (20.0)	3 (30.0)
Premature birth, n (%)	1 (10.0)	0
Subtype of *MMUT* mutation, n (%)		
mut$^-$	3 (30.0)	1 (10.0)
mut^0	7 (70.0)	9 (90.0)
Feeding tube present, n (%)	9 (90.0)	10 (100.0)
Nasogastric tube	5 (50.0)	4 (40.0)
Gastrostomy tube	5 (50.0)	6 (60.0)
Age at insertion of gastrostomy tube, months		
Mean (SD)	4.7 (4.1)	3.9 (4.2)
Range	1-11	0-11
Disease phenotype, n (%)		
Abnormal motor function[b]	7 (70.0)	8 (80.0)
Basal ganglia stroke	1 (10.0)	2 (20.0)
Coma	1 (10.0)	0
Failure to thrive	4 (40.0)	5 (50.0)
Fatigue	1 (10.0)	5 (50.0)
Language delay	7 (70.0)	8 (80.0)
Lethargy	7 (70.0)	8 (80.0)
Pancreatitis	1 (10.0)	4 (40.0)
Seizures	3 (30.0)	2 (20.0)
Age at transplant, years		
Mean (SD)	–	2.0 (1.6)
Range	–	0.6-6.2
Prescription medications, n (%)		
Antianemic preparations[c]	9 (90.0)	8 (80.0)
Antiprotozoals[d]	1 (10.0)	0
Blood substitutes and perfusion solutions[e]	1 (10.0)	1 (10.0)
Corticosteroids for systemic use[f]	0	1 (10.0)
Drugs for acid-related disorders[g]	1 (10.0)	1 (10.0)
General nutrients[h]	1 (10.0)	1 (10.0)
Other alimentary tract and metabolism products[i]	10 (100.0)	10 (100.0)
Vitamins[j]	2 (20.0)	2 (20.0)
All other therapeutic products[k]	1 (10.0)	0

Note: If a patient is eligible for both cohorts, the patient is counted in both cohorts separately.
[a]Patients had positive newborn screening results for severe MMA. [b]Includes gross or fine motor function. [c]Hydroxocobalamin, ferrous sulfate, cyanocobalamin, folic acid, or iron. [d]Metronidazole. [e]Arginine hydrochloride, sodium acetate, or sodium bicarbonate. [f]Prednisone. [g]Citric acid or sodium citrate acid. [h]Carbohydrates not otherwise specified (NOS), fats NOS, iron, linoleic acid, minerals NOS, potassium, protein, sodium, vitamins NOS, maltodextrin, or nutrients NOS. [i]Levocarnitine, valine, sodium benzoate, carglumic acid, isoleucine, levocarnitine hydrochloride, levoglutamine, or sodium phenylbutyrate. [j]Thiamine, biotin, colecalciferol, pyridoxine, or riboflavin. [k]Sodium benzoate or sodium phenylacetate.

Laboratory Parameters

- Mean alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, ammonia, prothrombin time, total bilirubin, estimated glomerular filtration rate, and methylmalonic acid are reported as multiples of the normal range to account for methodological variation in **Figure 1**

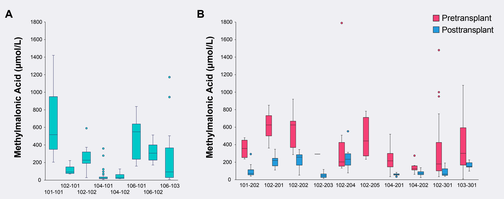
Figure 1. Laboratory Parameters During Study Period



Mean values for laboratory parameters (multiples of normal range) in cohorts 1 and 2, respectively: A and B, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), prothrombin time, and total bilirubin; C and D, estimated glomerular filtration rate (eGFR); E and F, ammonia; G and H, methylmalonic acid. Error bars represent standard deviations; for values without error bars, standard deviation was not calculable. For any time point where the n value is less than 3, the n value is highlighted as red text.

- Large variability in methylmalonic acid levels exists across patients and within individual patients over time (**Figure 2, A and B**)
  - In cohort 2, compared with pretransplant methylmalonic acid levels, the overall posttransplant methylmalonic acid levels were lower and had a narrower range (**Figure 2B**)

Figure 2. Patient Methylmalonic Acid Levels



Range of methylmalonic acid results in cohort 1 (A) and cohort 2 (B). Only 1 pretransplant methylmalonic acid result was available for patient 102-203, and no posttransplant methylmalonic acid results were available for patient 102-205. The minimum methylmalonic acid value for each patient is the lowest point in the graph; the maximum value is represented as the highest point in the graph and may be represented as an outlier. The ends of the boxes are the upper and lower quartiles, and the median is marked by a horizontal line within each box.

Growth Parameters

- For cohort 1, length/height remained below the median from baseline through 36 months; weight and body mass index (BMI) remained at or above the median starting at months 12 and 6, respectively; and head circumference measurements were variable throughout the 36 months (**Figure 3A**)
- For cohort 2, length/height and head circumference remained below the median from baseline through 36 months; weight and BMI increased at months 3 and 6 posttransplant but then declined to near median levels and remained there through month 36 (**Figure 3B**)
  - There was a significant increase in weight and BMI (*P*=0.0391) at 3 months posttransplant and a significant increase in BMI (*P*=0.0391) at 6 months posttransplant compared with baseline

Figure 3. Summary of Growth Parameters Over Time

Growth parameters are represented as *z*-scores based on the World Health Organization growth standards. *P=0.0391 vs baseline. Baseline (month 0) is the first nonmissing result post birth for cohort 1 (A) and the last nonmissing result prior to the liver transplant for cohort 2 (B). Error bars represent standard deviations; for data points without error bars, standard deviation was not calculable. For any time point where the n value is less than 3, the n value is highlighted as red text.

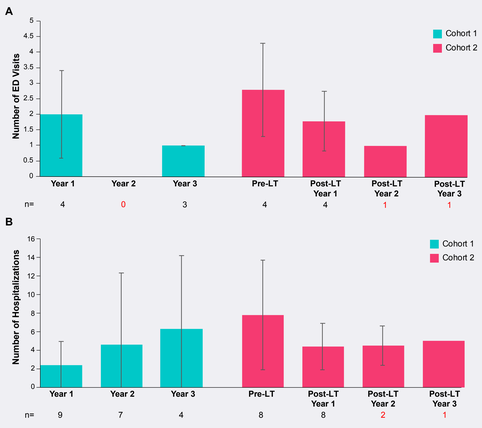
Dietary Management

- At baseline, the absolute value for protein intake was 1.8 g/kg for both cohort 1 and cohort 2
  - For cohort 1, the average daily protein intake consistently fluctuated above and below the baseline level over time (data not shown)
  - For cohort 2, the data on posttransplant protein intake were available for only 1 or 2 patients most months or not available at all, limiting the interpretation of the analysis

MMA- and Transplant-Related Healthcare Utilization

- Numbers of MMA- and transplant-related emergency department (ED) visits and hospitalizations are shown in **Figure 4**
  - Mean numbers of days in the ED were 2.5 (year 1) and 1.3 (year 3) for cohort 1 and 4.8 (pretransplant), 2.0 (year 1 posttransplant), 1.0 (year 2 posttransplant), and 2.0 (year 3 posttransplant) for cohort 2
  - No ED days were reported for cohort 1 in year 2
- In cohort 2, among patients whose healthcare utilization data were reported, there were no significant differences in MMA- or transplant-related ED visits, days in the ED, or number of hospitalizations between the pretransplant period and up to 3 years posttransplant
  - Data on healthcare utilization for years 2 and 3 posttransplant were available for only 1 or 2 patients, limiting the interpretation of the analyses past year 1

Figure 4. Summary of MMA- and Transplant-Related Healthcare Utilization



Mean number of emergency department (ED) visits (A) and mean number of hospitalizations (B) are shown for cohorts 1 and 2. LT, liver transplant. Error bars represent standard deviations; for columns without error bars, standard deviation was not calculable. For any time point where the n value is less than 3, the n value is highlighted as red text.

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Gregory M. Enns has served as a consultant for LogicBio Therapeutics, Inc, and has received personal fees outside the submitted work.
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