ACAPPELLA Study: Natural History Study of Classical HCU

Summary

Background

- Homocystinuria (HCU) is a rare hereditary disorder of amino acid metabolism characterized by accumulation of homocysteine, resulting in significant systemic toxicities affecting the vascular, skeletal, and ocular systems[1]
- Patients with Hcy levels >100 µM are at risk of severe multisystemic complications[2,3]
- The ACAPPELLA study is a prospective, longitudinal, multicenter, multinational, natural history study of patients aged 1-65 years with HCU[2]

Study Data

- At data cutoff (March 8, 2023), a total of 71 patients had participated in the ACAPPELLA study; mean duration of participation was 2.1 years[2]
- Despite SOC treatments, many patients showed suboptimal control of tHcy, with tHcy levels greater than clinically recommended thresholds[2]
- Patients exhibited multiple symptoms of HCU, including clinically significant deficits in bone density and cognitive function[2]

Background

HCU Disease State

Classical HCU is a rare hereditary disorder due to mutations in *CBS*, causing an inability to metabolize Hcy, a key molecule in several metabolic processes.[1,4] Deficiency of the CBS enzyme leads to increased levels of Hcy and its precursor, methionine, in plasma and tissue throughout the ocular, skeletal, vascular, and central nervous systems.[4] Symptoms can range from mild to severe, and may involve the eye, skeletal system, vascular system, and central nervous system. Expression of clinical signs is variable, with patients manifesting anywhere from 1 to all system impairments.[5]

Standard treatment of HCU seeks to control plasma Hcy concentrations and prevent thrombosis, and typically includes vitamin B6 (pyridoxine) therapy, a methionine-restricted diet, and vitamin B12 and folate supplements to maintain normal or near-normal tHcy levels. Betaine therapy is also a major form of treatment in adolescents and adults, although it is preferable that patients remain on a life-long metabolic diet.[5]

The ACAPPELLA Study

The ACAPPELLA study (NCT02998710) is a prospective, longitudinal, multicenter, multinational, natural history study in patients aged 1 to 65 years with clinically diagnosed HCU.[2,6] The primary study objective is to characterize the natural clinical course of HCU in patients currently under SOC treatments.[2] Primary outcome measures include changes in levels of tHcy, methionine, total Cys and Cth, patient-reported QOL, cognitive function, bone mineral density, and ocular health.[6] Up to 150 patients will be enrolled, with participation up to 6.5 years. A maximum 27 study visits occur every 3 months via in-home visits by mobile nurses or telemedicine. In-home visits include fasting blood draws, urine tests, and physical and cognitive examinations. Information is also collected regarding patient age, HCU genetics, growth and development, and metabolic values.[6,7]

Study Data

Interim Results

At data cutoff (March 8, 2023), a total of 71 patients had participated in the ACAPPELLA study; mean duration of participation was 2.1 (SD=1.1) years.[2]

Baseline Characteristics

The study sample included 37 adult and 34 pediatric patients; mean (SD) age was 32.5 (9.9) and 10.5 (3.6) years, respectively. Females comprised 50.7% of patients. Thirteen (18.3%) patients had <1 year of study participation, 41 (57.8%) patients had 1 to <3 years of participation, and 17 (23.9%) had participated from 3 to <6 years. Additional baseline characteristics are presented in **Table 1**.[2]

Table 1. Patient Baseline Characteristics

Category	Pediatric (N=34)	Adult (N=37)	Total (N=71)
Age (years), mean (SD)	10.5 (3.6)	32.5 (9.9)	22.0 (13.4)
Sex, n (%)			
Male	17 (50.0)	17 (45.9)	34 (47.9)
Female	17 (50.0)	19 (51.4)	36 (50.7)
Missing	0	1 (2.7)	1 (1.4)
Race, n (%)			
White	33 (97.1)	33 (89.2)	66 (93.0)
Black or African American	1 (2.9)	2 (5.4)	3 (4.2)
Not provided/missing	0	2 (5.4)	2 (2.8)
Duration of study (years), mean (SD)	2.2 (1.0)	1.9 (1.2)	2.1 (1.1)
Duration categories (years), n (%)			
<1	4 (11.8)	9 (24.3)	13 (18.3)
1 to <3	20 (58.8)	21 (56.8)	41 (57.8)
3 to <6	10 (29.4)	7 (18.9)	17 (23.9)

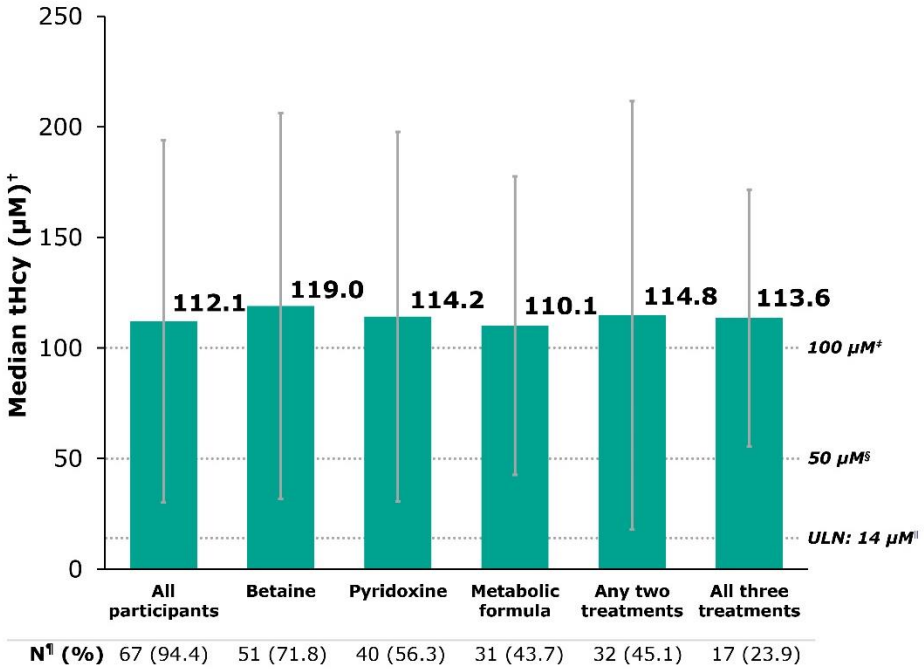
SD, standard deviation.

SOC therapies for HCU were utilized by study participants, either individually or in combination. Treatments included betaine (n=51; 72%), pyridoxine (n=40; 56%), metabolic formula (n=31; 44%), any combination of 2 (n=32; 45%), or 3 (n=17; 24%) treatments.[2]

Clinical Characteristics

Despite SOC utilization, mean tHcy levels were above the recommended clinical threshold for avoidance of HCU-related complications (<100 µM), indicating suboptimal metabolic control of tHcy (**Figure 1**).[2]

Figure 1. tHcy Levels per SOC Treatment



*Patients may have received other concomitant treatments not listed. †Median tHcy values were calculated for each subject using all available data over the first seven visits. For each subgroup, means were calculated from the median tHcy value of each participant and error bars represent SD. ‡Clinical threshold for minimizing HCU complications recommended by E-HOD guidelines.3§Clinically recommended threshold in pyridoxine-responsive patients (E-HOD).3 ULN provided by the Clinical Laboratory Improvement Amendments lab at the Center of Metabolomics, Institute of Metabolic Disease, Baylor Scott White Research Institute. ¶Data unavailable for four participants.
E-HOD, European Network and Registry for Homocystinurias and Methylation Defects; HCU, classical homocystinuria; SD, standard deviation; SOC, standard of care; tHcy, total homocysteine; ULN, upper limit of normal.

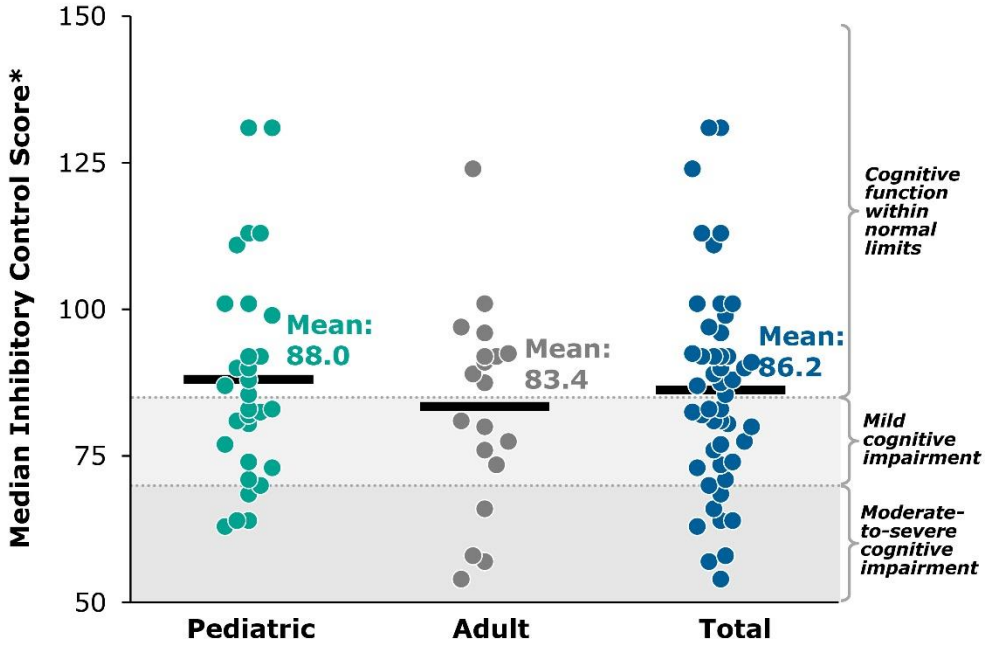
DXA evaluations of total body, spine, and hip revealed substantial deficits in bone mineralization. Total body deficits were found in 47% of patients; 13% had DXA scores indicating clinically significant osteoporosis. DXA results meeting the threshold for clinical osteopenia were found in patients for both hip (n=22; 43.1%) and spine (n=19; 38%).[2]

Cognitive function as assessed by the NIH Toolbox Cognition Battery found 35% of patients had median total composite scores consistent with clinically significant cognitive impairment. Among these patients, 19% demonstrated moderate to severe impairment. Median cognition composite

scores consistent with clinically significant cognitive impairment were found in 48% of patients, with 2% experiencing moderate to severe deficits.[2]

Among both pediatric and adult study participants, the largest cognitive deficit was in inhibitory control. Median scores indicating clinically significant cognitive impairment were found in 49% of patients, with 18% of patients demonstrating moderate to severe deficiencies (**Figure 2**).[2]

Figure 2. NIHTB-CB Inhibitory Control Results by Age Group



n/N (%) with median values meeting cognitive score threshold			
≤85	15/30 (50.0)	9/19 (47.4)	24/49 (49.0)
≤70	5/30 (16.7)	4/19 (21.1)	9/49 (18.4)

*Median scores were calculated for each subject using all available data over the first 7 visits. For each subgroup, means were calculated from the median Flanker Inhibitory Control score of each participant.

Abbreviations

CBS, cystathionine-β-synthase; Cth, cystathionine; Cys, cysteine; DXA, dual-energy X-ray absorptiometry; E-HOD, European Network and Registry for Homocystinurias and Methylation Defects; HCU, homocystinuria; Hcy, homocysteine; NIH, National Institutes of Health; NIHTB-CBI NIH Toolbox Cognition Battery; QOL, quality of life; SD, standard deviation; SOC, standard of care; tHcy, total homocysteine; ULN, upper limit of normal.

References

1. Skvorak K, Mitchell V, Teadt L, et al. An orally administered enzyme therapeutic for homocystinuria that suppresses homocysteine by metabolizing methionine in the gastrointestinal tract. *Mol Genet Metab*. 2023;139(4):1-8. doi:doi.org/10.1016/j.ymgme.2023.107653
2. Ficicioglu C, Chapman K, Lah M, et al. Clinical characterization of classical homocystinuria due to cystathionine beta-synthase deficiency: Results from the acappella study. Poster presented at: SSIEM; August 29 - September 1 2023; Jerusalem, Israel.
3. Morris AAM, Kozich V, Santra S, et al. Guidelines for the diagnosis and management of cystathionine beta-synthase deficiency. *J Inherit Metab Dis*. 2017;40:49-74. doi:10.1007/s10545-016-9979-0
4. Sellos-Moura M, Glavin F, Lapidus D, Evans K, Lew CR, Irwin DE. Prevalence, characteristics, and costs of diagnosed homocysinuria, elevated homoceyseine, and phenylketonuria in the United States: A retrospective claims-based comparison. *BMC Health Serv Res*. 2020;20(1):1-11. doi:doi:10.1186/s12913-020-5054-5.
5. Sacharow SJ, Picker JD, Levy HL. Homocysteinuria caused by cystathionine beta-synthase deficiency. In: Adam MP, Ardinger HH, Pagon RA, eds. *GeneReviews*. 1993-2023. https://www.ncbi.nlm.nih.gov/books/NBK1524
6. ClinicalTrials.gov. A multicenter, observational, prospective, natural history study of homocystinuria due to cystathionine beta-synthase deficiency in pediatric and adult patients (acappella). Updated January 17, 2023. Accessed November 26, 2023. https://clinicaltrials.gov/study/NCT02998710?term=ACAPPELLA%20CBS&rank=1
7. Data on file. Travere Therapeutics Inc; 2023.