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Long-Term Open-Label Study Evaluating Oral Miglustat Treatment in Patients With Neuronal Ceroid Lipofuscinosis Type 3

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Abstract

Objectives

Neuronal ceroid lipofuscinosis type 3 (CLN3) is a rare lysosomal storage disorder characterized by progressive neurodegeneration. No disease-modifying treatments are currently available. Miglustat, a substrate reduction therapy, has shown preclinical efficacy in CLN3 models (conference abstract). The aim of this study was to assess the long-term safety and clinical impact of miglustat in patients with CLN3 disease.

Methods

This was an open-label, single-center study conducted at Bambino Gesù Children's Hospital in Rome, Italy. Oral miglustat was titrated to 15 mg/kg/d or a maximum of 600 mg/d. Patients were assessed every 6 months using the Unified Batten Disease Rating Scale (UBDRS). The primary outcome was the annual rate of change in the UBDRS physical subscale. Clinical data were analyzed descriptively.

Results

Six patients (33% female) with a median age of 20.34 years (interquartile range [IQR] 18.25–23.84) were treated and followed for a median of 3.9 years (IQR 3.32–4.34). The mean annual change in the UBDRS physical score was +1.96 points per year (SD ± 0.80). Miglustat was well tolerated, with only mild, self-limiting gastrointestinal side effects observed.

Discussion

Miglustat showed a favorable safety profile and was associated with a slower rate of physical decline compared with historical controls. Limitations include small sample size, genetic heterogeneity, and open-label design.

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Introduction

Neuronal ceroid lipofuscinosis type 3 (CLN3) is a rare pediatric lysosomal storage disorder caused by biallelic pathogenic variants in the CLN3 gene.[1] It is characterized by progressive vision loss, cognitive decline, motor impairment, and epilepsy, ultimately leading to premature death.[2,3] No disease-modifying treatments are currently available. Miglustat (Zavesca), a substrate reduction therapy (SLT) approved for other lysosomal storage disorders,[4] inhibits glucosylceramide synthase, reducing lysosomal glycosphingolipid (GSL) accumulation.[5]

Preclinical data suggest a potential therapeutic role in CLN3 disease; however, these findings have not been published in any peer-reviewed format and are currently available only as a conference abstract,[6] and a clinical trial is currently ongoing.[7]

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In this study, we report 6 patients with CLN3 treated with miglustat for 3.9 years at standard doses, evaluating its effects using the Unified Batten Disease Rating Scale (UBDRS).[8,9] This is a long-term study of miglustat in CLN3, providing preliminary insights into its safety and potential impact on disease progression.

Methods

The aim of this open-label, single-center study, conducted at Bambino Gesù Children's Hospital in Rome, Italy, was to evaluate the safety and efficacy of the maximum tolerable dose of miglustat in individuals with CLN3 disease. Oral miglustat therapy was commenced in October 2023 and titrated over 1 month up to 15 mg/kg/d or a maximum of 600 mg in 3 divided doses (as approved for the treatment of Niemann-Pick type C disease).[4]

All consecutive patients with a genetically confirmed diagnosis of syndromic CLN3 disease were enrolled in the study. Follow-up visits were conducted every 6 months to assess clinical outcomes, safety, tolerability, and treatment efficacy. Clinical outcomes were evaluated using the UBDRS, administered by 2 experienced neurologists.

Descriptive statistics were used to summarize demographic and clinical characteristics of the study cohort. For each patient, the annual change in the UBDRS physical score was calculated by dividing the total score difference by the number of 6-month intervals and multiplying by 2. The mean and standard deviation of annual changes were then computed across all patients.

Standard Protocol Approvals, Registrations, and Patient Consents

The study was approved by the local ethical committee. Written informed consent was obtained from all participants or their legal guardians in accordance with the Declaration of Helsinki.

Data Availability

The data supporting the findings of this study are available from the corresponding author on reasonable request.

Results

A total of 6 patients, including 2 women, with a genetically confirmed diagnosis of CLN3 disease were enrolled in this study (Table). The median age at the time of inclusion was 20.34 years (interquartile range [IQR] 18.25–23.84; range 10.85–25.46). All participants exhibited the classic juvenile-onset form of CLN3 disease, with initial symptoms emerging at a median age of 6.22 years (IQR 5.17–7.43, range 4.21–8.52). By the time of the first evaluation, the median duration of the disease was 12.87 years (IQR 12.05–17.30, range 5.1–20.8). The median follow-up duration was 3.88 years (IQR 3.32–4.34, range 3.17–4.56).

All patients received miglustat treatment with titration up to a maximum dose of 600 mg per day, except for 1 participant (patient 2), who was maintained on a lower dosage of 300 mg per day.

Regarding physical assessment, the mean UBDRS physical subscale score was 38.5 (±22.31 SD, range 5–72) at baseline and 45.83 (±24.07 SD, range 8–80) at the final follow-up visit ($p = 0.0008$).

The overall mean annual change in the neurologic score was +1.96 points per year (±0.80 SD).

Additional UBDRS assessment results are detailed in the Table.

Regarding safety and tolerability, no significant adverse reactions were observed or reported during the study period, suggesting that miglustat was well tolerated across the cohort. Mild and transient gastrointestinal side effects were noted in a small subset of patients, with abdominal bloating occurring in 2 individuals and diarrhea reported by 2 patients. These symptoms were self-limiting and resolved without the need for intervention. In addition, renal function parameters and liver enzyme levels remained within normal reference ranges throughout the study, including at baseline, during follow-up, and at the final assessment (Figure).

Discussion

Although the precise role of CLN3 remains unclear, evidence suggests its involvement in lipid homeostasis, particularly in lysosomal clearance of GSLs such as globotriaosylceramide (Gb3) and glycerophosphodiesters.[10,11] Gb3 accumulation has been observed in CLN3 patient tissue and deficient cell models, with increased ganglioside GM3 levels in murine models.[12]

Miglustat, a SRT, has been investigated for the treatment of CLN3 disease. As a glucosylceramide synthase inhibitor, it crosses the blood-brain barrier, reducing GSL accumulation, mitochondrial ATP synthase subunit c deposition, and excitotoxicity while improving cellular function in CLN3 models.[6]

A phase I/II clinical trial investigating miglustat in patients with CLN3 aged 17 years and older is currently underway.[7]

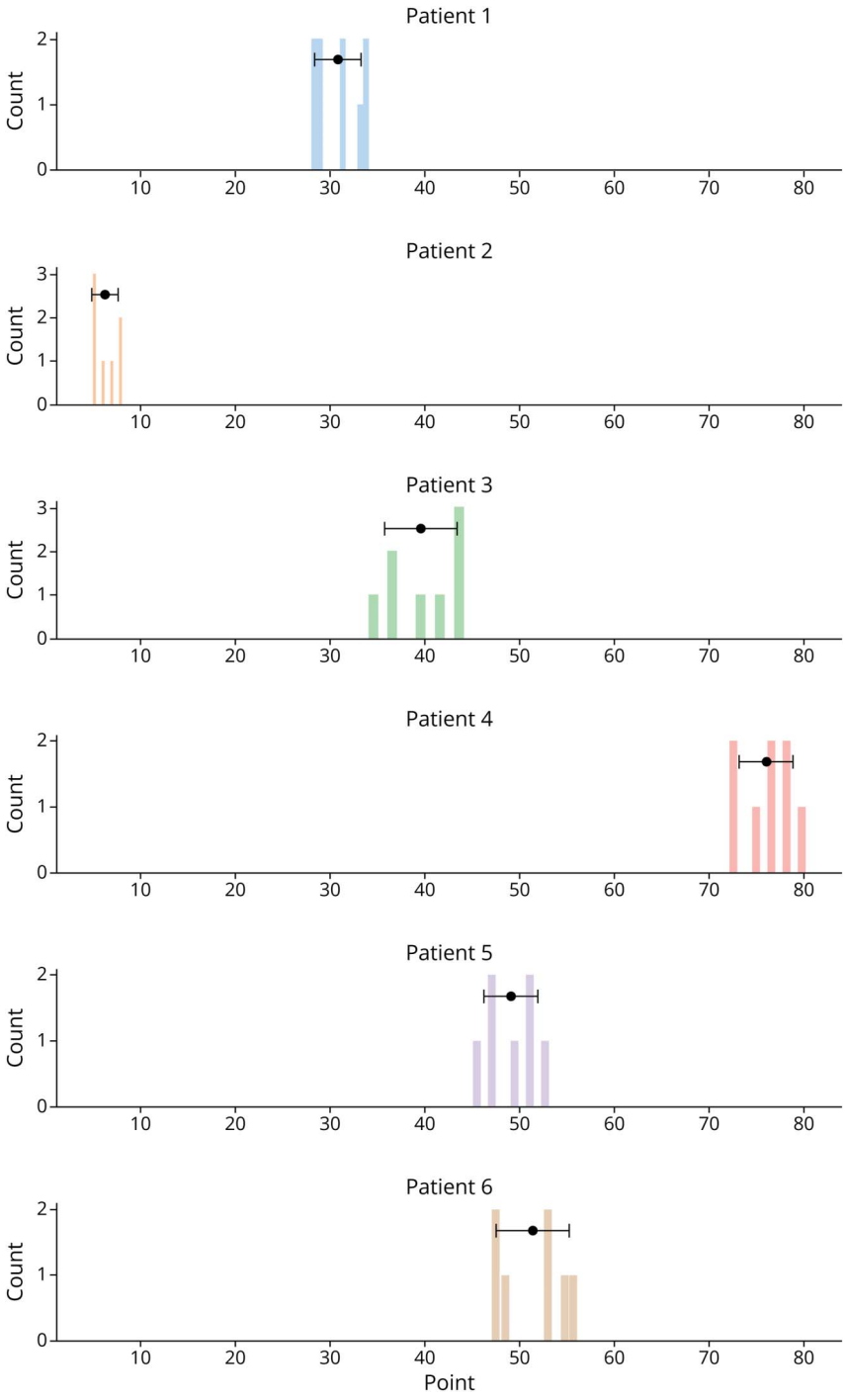
The findings of this study provide valuable insights into the potential therapeutic role of miglustat in the management of CLN3 disease. The median follow-up duration was approximately 4 years, providing an extensive observation window to assess the effects of miglustat over time.

Table Patient Characteristics

Patient	Genetic variant	Zygosity	Disease onset, y	Disease duration, y	Age at baseline, y	Follow-up, y	UBDRS							
							Physical assessment: baseline	Physical assessment: LFV	Seizure assessment: baseline	Seizure assessment: LFV	Behavior assessment: baseline	Behavior assessment: LFV	CGI score overall: baseline	CGI score overall: LFV
1	c.631C>T, p.Gln211Ter; 1.02-kb deletion encompassing exons 7 and 8	Compound heterozygous	4.97	12.9	17.55	4.56	28	34	0	4	3	4	4	4
2	c.555del, p.Ser186fs	Homozygous	5.75	5.10	10.85	3.78	5	8	0	0	0	1	2	2
3	c.1115_1118dup, p.Val374fs	Homozygous	4.21	20.8	25.01	3.98	34	44	0	0	19	25	4	4
4	c.424delG, p.Val142fs	Homozygous	6.69	18.77	25.46	4.46	72	80	8	10	8	11	5	5
5	c.631C>T, p.Gln211Ter	Homozygous	7.68	12.66	20.34	3.17	45	53	2	2	11	15	4	5
6	c.631C>T, p.Gln211Ter	Homozygous	8.52	11.85	20.34	3.17	47	56	2	2	11	13	4	5

Abbreviations: CGI = Clinical Global Impression; LVF = last follow-up visit; UBDRS = Unified Batten Disease Rating Scale.

Figure Annual Rate of Change in UBDRS Scores in Patients With CLN3 Treated With Miglustat



Each bar represents the annual mean change in the UBDRS score for an individual patient. Error bars denote the standard deviation relative to the cohort mean. UBDRS = Unified Batten Disease Rating Scale.

Our findings estimated a progression rate of 1.96 points per year (SD ±0.80), indicating a markedly slower and more variable disease course compared with previous natural history studies. In a previous study,[13] physical decline was reported at a rate of approximately 2.86 points per year (95% CI 2.27–3.45, $p < 0.00019$), while Masten et al.[14] found a similar rate of 3.11 ± 0.28 points per year. Likewise, Wibbeler et al.[9] observed a decline of 3.06 points per year ($R^2 = 0.66$) in a cohort of 13 patients with genetically confirmed CLN3.

The observed slower deterioration in our cohort suggests that miglustat may influence the rate of physical impairment progression in patients with CLN3, and the stronger association observed with age at start of miglustat therapy, despite not reaching statistical significance, may indicate a potential impact of treatment timing on disease progression.

It is important to note that miglustat demonstrated a favorable safety and tolerability profile over the course of this study.

The considerably lower rate of progression observed in our cohort may reflect interindividual variability, a shorter follow-up period, or differences in genetic background and disease severity. Notably, only 1 patient carried the common CLN3 deletion, unlike the 74% reported in natural history cohorts.[13] This marked genotypic difference between our cohort and those described in the literature may further hinder comparability, considering the possible genotype-phenotype correlations.

Moreover, these results highlight the necessity of early diagnosis in CLN3 disease to facilitate timely intervention, which could enhance therapeutic efficacy and ultimately improve patient outcomes.

In conclusion, our findings contribute to the growing body of evidence supporting the potential role of miglustat as a therapeutic option for CLN3 disease. While the results suggest a slower rate of physical decline in treated patients compared with historical data, confirmation through larger, randomized, placebo-controlled trials are essential.

Early diagnosis and the development of reliable biomarkers to monitor disease progression and treatment remain paramount in maximizing therapeutic benefits, and timely initiation of treatment may offer the best opportunity to alter disease trajectory.

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Author Contributions

N. Pietrafusa: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. M. Trivisano: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. C. Calabrese: analysis or interpretation of data. A. De Dominicis: analysis or interpretation of data. S. Cappelletti: major role in the acquisition of data; analysis or interpretation of data. C. Correale: major role in the acquisition of data; analysis or interpretation of data. L. Salimbene: major role in the acquisition of data; analysis or interpretation of data. L. Vallesi: major role in the acquisition of data; analysis or interpretation of data. T. Corsetti: major role in the acquisition of data; analysis or interpretation of data. N. Specchio: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design.

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Disclosure

The authors report no relevant disclosures. Go to Neurology.org/N for full disclosures.

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