Survival analysis in untreated patients with thymidine kinase 2 deficiency (TK2d) aged ≤12 years at TK2d symptom onset: findings from the largest international TK2d dataset

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Introduction

- Thymidine kinase 2 deficiency (TK2d) is an autosomal recessive, mitochondrial disease associated with progressive proximal myopathy, bulbar weakness, respiratory insufficiency and early death[1]
- The prevalence (25th percentile, 75th percentile) of TK2d is estimated at 1.64 (0.5, 3.1) patients per million people worldwide,[2] although many patients are not identified owing to underdiagnosis and misdiagnosis[3]
- TK2d presents as a continuous clinical spectrum with varying age of symptom onset[1]
  - Typically, the earlier symptoms appear, the faster the disease progresses; patients with age of TK2d symptom onset ≤12 years tend to experience rapid disease progression resulting in early death[3]
- The rapid progression of TK2d necessitates comprehensive management by a multidisciplinary team of healthcare professionals and imposes a significant burden on patients and caregivers[4]
  - Currently, there are no approved treatments for TK2d, and management is limited to supportive care[4]
  - Doxecitine and doxribtimine, an oral pyrimidine nucleoside therapy containing deoxycytidine and deoxythymidine, is under review by health authorities for use in TK2d
  - In patients with age of TK2d symptom onset ≤12 years, pyrimidine nucleos(t)ide therapy was generally well tolerated, significantly decreased the risk of mortality by 87–95% and increased survival time[5]
- Given the ultra-rare nature of TK2d, data on natural disease progression are scarce and no TK2d-specific registries exist

Objective

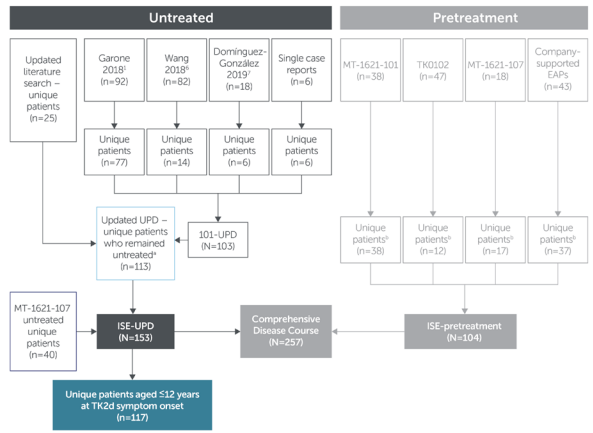
- Here we describe the characteristics and survival of patients with TK2d and age of symptom onset ≤12 years who were not treated with pyrimidine nucleos(t)ides
  - Results on functional outcomes in this population, including developmental motor milestones and use of ventilatory and enteral feeding tube support will be presented in session PA16 on 11 July 2025 at 10:30–12:15

Methods

Study design

- A global Comprehensive Disease Course dataset of untreated patients with TK2d was generated from various data sources (**Figure 1**)
  - The Comprehensive Disease Course dataset comprised data from untreated patients (Integrated Summary of Efficacy [ISE]-Untreated Patient Database [UPD]) and pretreatment data from patients with TK2d later treated with pyrimidine nucleos(t)ides (ISE-pretreatment)
  - The ISE-UPD contained data from a comprehensive literature review of case studies conducted in June 2019 and updated in October 2021, as well as data from a retrospective chart review study (MT-1621-107 [NCT05017818])
  - The ISE-pretreatment dataset incorporated pretreatment data from three clinical trials (MT-1621-101 [NCT03701568], TK0102 [NCT03845712], MT-1621-107) and company-supported Expanded Access Programs [EAPs])
- Only the ISE-UPD (153/257 patients from the Comprehensive Disease Course dataset) was included in survival analyses; the ISE-pretreatment group was excluded to avoid the introduction of immortal time bias
  - Data presented in this poster are from the 117 patients in the ISE-UPD with an age of TK2d symptom onset ≤12 years
- Data were cross-checked to remove duplicates to the greatest extent possible

Figure 1. Study analysis populations



[a]Of 128 unique patient sources from the literature, 1 patient without genetic confirmation of a TK2d diagnosis was excluded from the updated-UPD group, while 14 patients were excluded because they later received treatment. [b]Patients who received treatment in another study were not included to avoid duplication of data to the greatest extent possible.
EAP, Expanded Access Program; ISE, Integrated Summary of Efficacy; TK2d, thymidine kinase 2 deficiency; UPD, Untreated Patient Database.

Outcomes

- Outcomes included survival time from birth and from TK2d symptom onset

Statistical analysis

- Kaplan–Meier analysis was used to estimate the median (95% confidence interval [CI]) time from birth and from TK2d symptom onset to death
  - Patients with no event data or missing dates were censored at time point zero
  - In time-to-event analyses, patients who did not experience the event were censored at age last known alive or treated (if applicable), whichever occurred first
- Missing or partial dates were imputed as per the rules specified in the statistical analysis plan for each source dataset; no other imputation was performed

Results

Patient characteristics

- In total, 117 patients from the ISE-UPD had an age of TK2d symptom onset ≤12 years and were included in this study (**Table 1**)
  - 53.0% of patients were male and the median (minimum, maximum) age at TK2d symptom onset was 1.2 (0.0, 11.0) years

Survival analyses

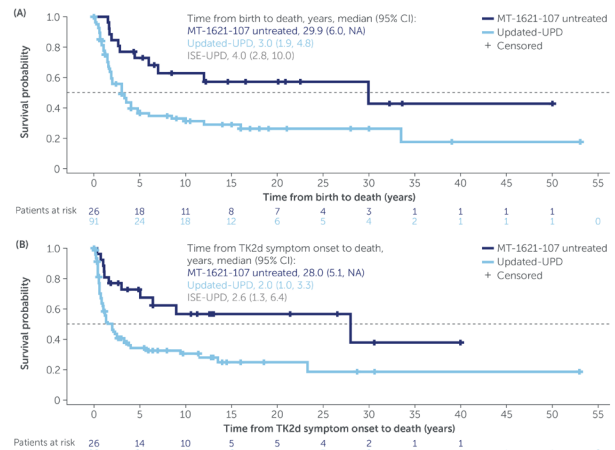
- Among patients with age of TK2d symptom onset ≤12 years, 66/117 patients (56.4%) from the ISE-UPD died, with a median (first quartile, third quartile) age at death of 1.9 (1.0, 3.5) years
- In the ISE-UPD, Kaplan–Meier estimates of median (95% CI) time from birth and from TK2d symptom onset to death were 4.0 (2.8, 10.0) years and 2.6 (1.3, 6.4) years, respectively (**Figure 2**)

Table 1. Demographics and disease characteristics of patients with TK2d and age of symptom onset ≤12 years

	ISE-UPD (N=117)
Sex, n (%)	
Male	62 (53.0)
Female	53 (45.3)
Missing	2 (1.7)
Race,[a] n (%)	
White	24 (20.5)
Other	2 (1.7)
Missing/not reported	91 (77.8)
Ethnicity, n (%)	
Hispanic or Latino	12 (10.3)
Not Hispanic or Latino	14 (12.0)
Missing/unknown/not reported	91 (77.8)
Geographic region of residence,[a] n (%)	
Europe	20 (17.1)
Rest of world	48 (41.0)
Missing/unknown	49 (41.9)
Age of TK2d symptom onset, years	n=108
Median (min, max)	1.2 (0.0, 11.0)
Q1, Q3	0.5, 2.0
Age at genetic confirmation, years	n=59
Median (min, max)	5.2 (0.0, 56.4)
Q1, Q3	2.0, 14.4
Time from TK2d symptom onset to genetic confirmation, months	n=59
Median (min, max)	38.1 (–5.9, 556.4)[b]
Q1, Q3	9.4, 129.1

[a]Owing to the ultra-rare nature of TK2d and the small number of patients, some details relating to race and country of residence were grouped for reporting purposes, to minimize the risk of patient reidentification. [b]Negative values for time from TK2d symptom onset to genetic confirmation indicate that genetic confirmation took place before the onset of disease symptoms.
ISE, Integrated Summary of Efficacy; max, maximum; min, minimum; Q1, first quartile; Q3, third quartile; TK2d, thymidine kinase 2 deficiency; UPD, Untreated Patient Database.

Figure 2. Product-limit survival estimates of time from (A) birth and (B) TK2d symptom onset to death in the MT-1621-107 untreated and updated-UPD populations with age of symptom onset ≤12 years



Patients censored at time point zero (event data not collected, no dates or missing period start or end dates) or at a later point in time (last known alive). The MT-1621-107 untreated and updated-UPD datasets are subpopulations of the ISE-UPD dataset. The ISE-UPD dataset is not plotted, given that it aggregates already plotted population datasets.
CI, confidence interval; ISE, Integrated Summary of Efficacy; NA, not available; TK2d, thymidine kinase 2 deficiency; UPD, Untreated Patient Database.

Conclusions and Outlook

The Comprehensive Disease Course dataset represents the largest single source of natural disease course data for patients with TK2d

Our findings demonstrate reduced survival in untreated patients with TK2d and age of symptom onset ≤12 years, with data suggesting that patients face a high risk of early death in the 3 years after TK2d symptom onset

Understanding the natural disease course of TK2d may aid management strategies and inform the development of studies to investigate new treatment options

Limitations

- Study limitations included the high proportion of missing data for some variables, owing to the retrospective nature of the study in this ultra-rare disease, and the possibility for bias introduced by the requirement for genetic confirmation of pathogenic thymidine kinase gene variants, which excluded patients who died before genetic testing was available

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References: 1. Garone C, *et al. J Med Genet* 2018;55:515–21. 2. Ma Y, *et al. Value Health* 2023;26 (12 Suppl):S229. 3. Berardo A, *et al. J Neuromuscul Dis* 2022;9:225–35. 4. Wang J, *et al.* 2018. In: Adam MP, Feldman J, Mirzaa GM, *et al.*, editors. GeneReviews® [internet]. Seattle (WA): University of Washington, Seattle; 2018. Available from: https://www.ncbi.nlm.nih.gov/books/NBK114628/ (Accessed 2 April 2025). 5. Hirano M, *et al.* Survival analyses in patients with thymidine kinase 2 deficiency aged ≤12 years at symptom onset who received pyrimidine nucleos(t)ide therapy [poster]. Presented at the 2025 Muscular Dystrophy Association (MDA) Clinical & Scientific Conference, Dallas, TX, USA; 16–19 March 2025. 6. Wang J, *et al. Mol Genet Metab* 2018;124:124–30. 7. Domínguez-González C, *et al. Orphanet J Rare Dis* 2019;14:100.

Disclosures: Cristina Domínguez-González serves on an advisory board of UCB; has received funding from UCB to cover travel expenses to medical conferences and as a speaker; and has received funding from UCB for research projects related to TK2d. **Andrés Nascimento** serves on the advisory board of UCB; has received speaker and consultancy fees from Novartis, PTC Therapeutics, Roche and Sarepta Therapeutics; and is an investigator on clinical trials sponsored by Biogen, BioMarin, Italfarmaco, Roche, Sanofi, Sarepta Therapeutics, Scholar Rock (SRK) and TAMDMD. **Yuanjun Ma** is an employee of UCB. **Nada Boudiaf** is an employee of Covance Laboratories, under contract to UCB. **Richard Kim** is a consultant under contract to UCB. **Susan VanMeter** is an employee of and stockholder in UCB. **Marcus Brunnert** is an employee of UCB. **Michio Hirano** serves on an advisory board of UCB; has received research support, honoraria or both from Astellas Pharma, Entrada Therapeutics, Modis Therapeutics (a wholly owned subsidiary of Zogenix/UCB), Precision BioSciences and Stealth BioTherapeutics; and has received grant support from the Department of Defense (FPA W81XWH2010807), the J. Willard and Alice S. Marriott Foundation, the Muscular Dystrophy Association (577392) and the National Institutes of Health (NIH; U54 NS078059 and P01 HD32062). **Michio Hirano** is also on the scientific and medical advisory boards of the Barth Syndrome Foundation and the United Mitochondrial Disease Foundation, and he is on the Research Advisory Committee of the Muscular Dystrophy Association. Columbia University Irving Medical Center (CUIMC) has a patent for deoxynucleoside therapies for mitochondrial DNA depletion syndrome including TK2 deficiency, which is licensed to Modis Therapeutics, a wholly owned subsidiary of Zogenix/UCB; this relationship is monitored by an unconflicted external academic researcher. **Michio Hirano** is a co-inventor of this patent. CUIMC has received royalty payments related to the development and commercialization of the technology: **Michio Hirano** has received shares of the royalty payments following Columbia University policies.