Outcomes in participants with infantile-onset Niemann-Pick disease type C receiving prompt and sustained treatment with adrabetadex

Poster 25

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BACKGROUND

- Niemann-Pick disease type C (NPC) is a rare, progressive, neurodegenerative genetic disorder caused by impaired cholesterol trafficking, resulting in cholesterol accumulation and downstream cellular dysfunction.[1]
- Infantile-onset NPC (I-NPC; neurological symptom onset <6 years of age) is associated with the most rapid neurodegeneration, accelerated clinical progression, and markedly increased risk of premature mortality.[1]
- FDA-approved treatments for the neurological manifestations of NPC are indicated only for patients ≥2 years of age (arimoclomol) or ≥15 kg (levacetylleucine), leaving limited treatment options for individuals with early I-NPC.[2,3]
- Adrabetadex is an investigational intrathecal therapy for I-NPC and the only therapy designed to directly target accumulated intracellular cholesterol in the CNS, the central pathogenic driver of NPC, by restoring cholesterol trafficking.
- Adrabetadex is also the only therapy shown to improve overall survival in both early and late I-NPC and has been associated with reduced neurological disease progression.[4]
- **Because cholesterol accumulation has been shown to occur prior to progressive neuronal cell loss and neurodegeneration,[5,6] early targeting of cholesterol trafficking may improve long-term clinical outcomes in I-NPC.**
- In an observational cohort of individuals with NPC receiving routine clinical care, an annualized progression rate of 1.5 units/year was observed on the 5-domain NPC Clinical Severity Scale (NPCCSS).[7]
- This analysis evaluates outcomes in participants with I-NPC receiving prompt versus delayed adrabetadex treatment following diagnosis.

OBJECTIVES

To describe disease progression in participants with I-NPC who received sustained adrabetadex treatment for ≥5 years, stratified by whether treatment was initiated within or after 1 year of neurological symptom onset.

METHODS

- Individuals with I-NPC were eligible to participate in an intrathecal adrabetadex expanded access program (EAP) that was initiated in 2013.
- In the EAP, the adrabetadex dose started at 200 mg or 400 mg based on age every 2 weeks with stepwise titration up to 1200 mg in the initial protocol or 900 mg in the later revision, and dose adjustments were allowed.[4]
- Outcome measures included the rescored 4-domain NPCCSS (R4DNPCCSS) score, which assesses ambulation, fine motor skills, speech, and rescored swallowing.[8]
- The EAP population was surveyed for participants with disease onset <6 years of age and who had sustained treatment for ≥5 years.
- Change from baseline in R4DNPCCSS score was summarized for participants treated with adrabetadex within <1 year (prompt treatment) versus ≥1 year (delayed treatment) from neurological onset.

RESULTS

Baseline characteristics

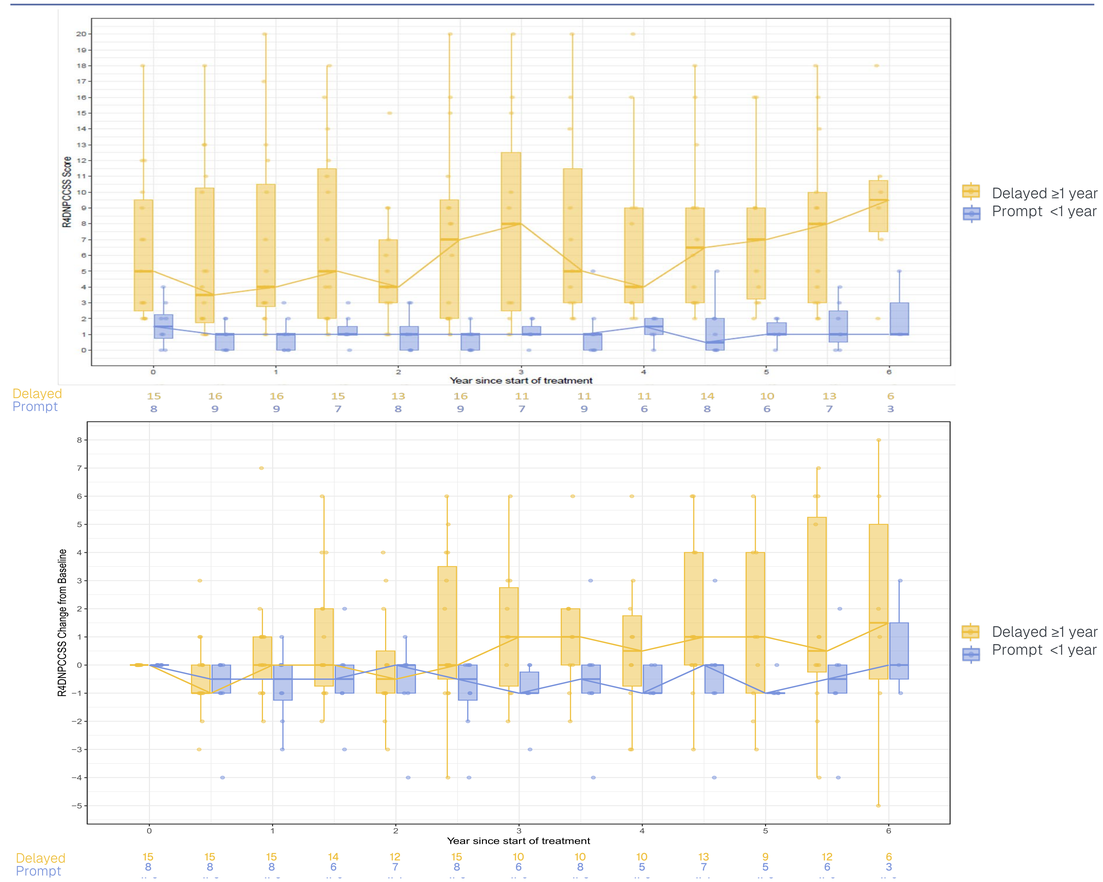
- A total of 25 participants were included (prompt treatment: n=9; delayed treatment: n=16) (Table 1).
- Age at neurological onset ranged from 0.8 to 5 years in the prompt group and from birth to 5 years in the delayed group.
- Time from onset to initiation of adrabetadex ranged from 0.2 to 0.9 years (prompt treatment group) and 1.0 to 12.2 years (delayed treatment group).
- Duration of treatment ranged from approximately 5.3 to 8.7 years and 5.3 to 11.1 years for the prompt and delayed treatment groups, respectively.
- Median (Q1, Q3) baseline R4DNPCCSS score was lower in the prompt treatment group vs the delayed treatment group: 1.5 (0.50, 2.5) vs 5.0 (2.0, 10.0).
- Mean age of neurological symptom onset (SD) was 2.11 (1.563) years in the prompt treatment group and 2.65 (1.494) years in the delayed treatment group.
- Participants with a delayed treatment initiation started receiving adrabetadex an average of 4.5 years following neurological onset; those with prompt treatment initiation started adrabetadex an average of 0.59 year after neurological onset.

Table 1. Baseline Demographics and Disease Characteristics

Baseline Characteristics	Treatment initiation <1 year from Onset (n=9)	Treatment initiation ≥1 year from Onset (n=16)
Age at neurological symptom onset, years		
Mean (SD)	2.11 (1.563)	2.65 (1.494)
Median (Q1, Q3)	1.67 (0.75, 3.00)	2.75 (1.50, 4.00)
Age at adrabetadex treatment start, years		
Mean (SD)	2.70 (1.614)	7.15 (3.838)
Median (Q1, Q3)	1.92 (1.68, 3.19)	6.52 (4.00, 8.42)
Sex, n (%)		
Male	5 (55.6)	9 (56.3)
Female	4 (44.4)	7 (43.8)
Race		
White	9 (100)	15 (93.8)
Multiple	0	1 (6.3)
Miglustat use at Baseline, n (%)		
Yes	1 (11.1)	9 (56.3)
No	8 (88.9)	7 (43.8)
Duration from onset to treatment, years		
Mean (SD)	0.59 (0.324)	4.50 (3.308)
Median (Q1, Q3)	0.69 (0.34, 0.88)	3.93 (2.08, 5.12)
R4DNPCCSS Baseline Value	n = 8	n = 15
Mean (SD)	1.63 (1.408)	6.47 (4.868)
Median (Q1, Q3)	1.50 (0.50, 2.50)	5.00 (2.00, 10.00)
Duration of treatment exposure, weeks		
Mean (SD)	348.37 (54.297)	397.23 (93.427)
Median (Q1, Q3)	340.29 (326.43, 360.43)	398.43 (310.14, 441.64)

Note: R4DNPCCSS - Composite Outcome (Ambulation, Speech, Fine Motor, Rescored Swallowing).
Abbreviations: SD=Standard Deviation, Q1=First Quartile, Q3=Third Quartile.

Figure 1. R4DNPCCSS Absolute (top) and Change from Baseline (bottom) Over Time



CONCLUSIONS

- Both prompt and delayed adrabetadex treatment were associated with slower disease progression relative to published natural history data.
- Participants who initiated adrabetadex within 1 year of neurological symptom onset demonstrated numerically lower R4DNPCCSS progression from baseline scores compared with later treatment initiation.
- These data suggest that early initiation of treatment with adrabetadex within 1 year of neurological symptom onset may result in greater long-term clinical benefit in I-NPC, consistent with the earlier targeting of accumulated intracellular cholesterol during ongoing neurodegeneration.
- Given the rapid progression, high unmet need, and limited treatment options in the youngest patients with I-NPC, findings support prompt initiation and sustained treatment with adrabetadex as a foundational therapeutic approach following diagnosis.

References

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