Reductions in oculogyric crisis duration and frequency in children with aromatic L-amino acid decarboxylase deficiency treated with eladocagene exuparvovec gene therapy: results from 3 clinical trials

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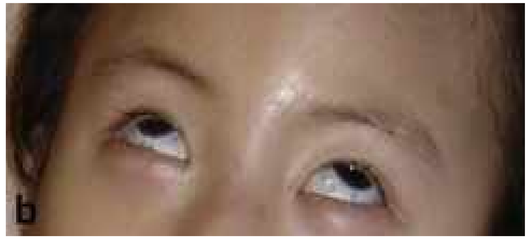
Poster #151

Introduction

- Aromatic L-amino acid decarboxylase (AADC) deficiency is a rare autosomal recessive disorder caused by mutations in the dopa decarboxylase (*DDC*) gene encoding the AADC enzyme, resulting in marked dopamine loss that impedes normal motor development.[1,2]
- A common feature of AADC deficiency is the presence of oculogyric crises (OGCs), which are frequently linked to decreased dopamine levels.[3]
- OGCs are characterized by involuntary eye movements due to dystonic spasms of ocular muscles.[4]
- Eyes are frequently directed upward during OGC episodes (**Figure 1**).[4]
- Episodes may last anywhere from minutes to hours.[4]

Figure 1. Representative example of oculogyric crisis[2]



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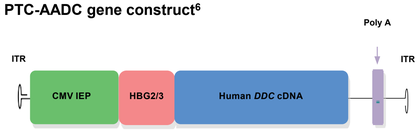
- OGCs may also be accompanied by limb stiffness, torso rigidity, and autonomic signs.[3]
- Eladocagene exuparvovec (PTC-AADC) is a gene therapy consisting of a recombinant adeno-associated viral vector serotype 2 containing the human cDNA encoding the AADC enzyme (**Figure 2**).
- PTC-AADC was studied in patients with AADC deficiency in 2 clinical trials and 1 compassionate use trial.
- Earlier data from these trials (AADC-CU/1601; AADC-010, NCT01395641; AADC-011, NCT02926066) demonstrated overall efficacy and safety of gene therapy with PTC-AADC in patients with AADC deficiency.[5]

Figure 2: PTC-AADC gene construct[6]



CMV IEP, human cytomegalovirus immediate-early promoter; hAADC, human DDC cDNA; HBG2/3, human beta globin partial intron 2/partial exon 3; ITR, adeno-associated virus serotype 2 inverted terminal repeat; Poly A, polyadenylation-containing sequence.

Purpose

Here we present data from 2 clinical trials and 1 compassionate use trial on the efficacy of intraputaminal infusion of PTC-AADC on the duration and frequency of OGC episodes in patients with AADC deficiency for ≤12 months post-treatment (at 26 February 2020 cutoff).

Methods

- PTC-AADC was administered as a bilateral infusion in the putamen of 28 children with AADC deficiency in 3 single-centre clinical trials (AADC-CU/1601 [compassionate use trial; 8 patients; completed], AADC-010 [phase 1/2 trial; 10 patients; completed] and AADC-011 [phase 2b trial; 10 patients to date; ongoing]).
- Patients were included in the trials if the following criteria were fulfilled:
  - Diagnosis of AADC deficiency indicated by characteristic cerebrospinal fluid (CSF) neurotransmitter metabolite profile and confirmed via enzyme activity test or genetic analysis of the *DDC* gene
  - Exhibited classical clinical characteristics of AADC deficiency, including OGC episodes, hypotonia and developmental retardation
  - Age >2 years
  - Parents or guardians agreed to cooperate and signed informed consent.
- Patients received a total dose of 1.8×10^{11} vg (n=21) or 2.4×10^{11} vg (n=7; AADC-011, patients aged <3 years).
- The percentage of patients with reported OGC episodes was calculated from case report forms of patients assessed at baseline and scheduled visits after surgery.
- Caregivers reported and recorded information related to OGC episodes in the OGC diary at baseline, up to 3 months, or up to 12 months after surgery.
- Duration (h/wk), frequency (episodes/wk) and percentage of time spent experiencing OGC episodes were calculated at baseline and 3 to 12 months after gene therapy.
- Due to the fluctuation of weekly data, the duration of OGC activity is expressed as the average frequency and duration of 5-week data at baseline, month 3, month 6, month 9 and month 12.
  - Baseline was defined as the average of data ≤5 weeks before gene therapy.
  - Post-gene therapy timepoints include data from 2 weeks prior to the timepoint, the week of that timepoint and 2 weeks after the selected timepoint.
- The percentage of time per week spent in OGC episodes for each patient was calculated as the total duration of all episodes within the 5-week interval divided by the total hours for that 5-week interval.
- The duration of OGC episodes (h/wk) was calculated by multiplying the percentage of OGC episodes per week by 168 hours.
- Frequency of OGC episodes (number of episodes/wk) was calculated as the average of the 5-week data.

Results

Patient demographics

- Baseline OGC diaries were provided for 22 patients, from which OGC episode data were collected.
- OGC episode data were summarized at 3 months (n=20), 6 months (n=12), 9 months (n=12) and 12 months (n=8) after PTC-AADC gene therapy.
- Baseline characteristics of full study populations are shown in **Table 1.**

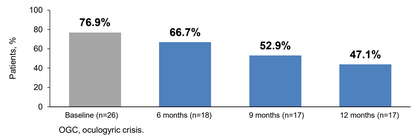
Table 1. Baseline characteristics of eladocagene exuparvovec study population[a]

	AADC-CU/1601 (N=8)	AADC-010 (N=10)	AADC-011 (N=10)	Total (N=28)
Age at symptom onset, n (%)				
≤6 mo	2 (25.0)	9 (90.0)	7 (70.0)	18 (64.3)
≤12 mo	0 (0)	1 (10.0)	3 (30.0)	4 (14.3)
>12 mo	5 (62.5)	0 (0)	0 (0)	5 (17.9)
Unknown	1 (12.5)	0 (0)	0 (0)	1 (3.6)
Age at gene therapy, n (%)				
<2 y	0 (0)	1 (10.0)	4 (40.0)	5 (17.9)
2–<6 y	5 (62.5)	5 (50.0)	6 (60.0)	16 (57.1)
6–<12 y	3 (37.5)	4 (40.0)	0 (0)	7 (25.0)
Sex, n (%)				
Male	3 (37.5)	5 (50)	6 (60)	14 (50.0)
Female	5 (62.5)	5 (50)	4 (40)	14 (50.0)
Race, n (%)				
Asian-Chinese	0 (0)	9 (90)	7 (70)	16 (57.1)
White	0 (0)	1 (10)	0 (0)	1 (3.6)
Asian-Other	8 (100)	0 (0)	3 (30)	11 (39.3)

Percentage of patients with reported OGC episodes

The percentage of patients with reported OGC episodes decreased following gene therapy from 76.9% (N=26) at baseline to 66.7% (n=18) at month 6, 52.9% (n=17) at month 9 and 47.1% (n=17) at month 12 (**Figure 3**).

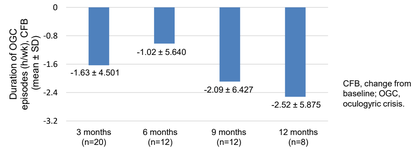
Figure 3. Percentage of patients with reported OGCs



Duration of OGC episodes

Mean duration of OGC episodes decreased compared to baseline as early as 3 months post-gene therapy and continued to decrease through 12 months (**Figure 4**). Mean duration of OGC episodes at baseline was 11.87 hours/week (N=22).

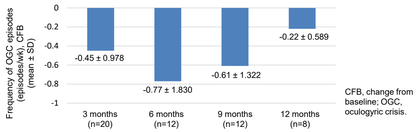
Figure 4. Duration of OGC episodes following PTC-AADC gene therapy, CFB



Frequency of OGC episodes

Frequency of OGC episodes also declined following gene therapy compared to baseline (**Figure 5**). Mean frequency of OGC episodes at baseline was 2.28 episodes/week (N=22). Mean duration of the OGC episodes decreased from months 3–12.

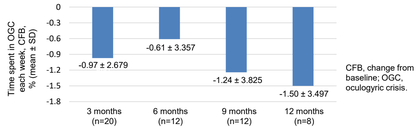
Figure 5. Frequency of OGC episodes following PTC-AADC gene therapy, CFB



Percentage of time spent in OGC episodes

The percentage of time spent in OGC episodes each week decreased following gene therapy through month 12 (**Figure 6**). The percentage of time experiencing OGC at baseline was 7.07% (N=22).

Figure 6. Percentage of time spent in OGCs each week, CFB



Safety

- Treatment-emergent adverse events (TEAEs) experienced in the treated population are shown in **Table 2,** and the most common TEAEs (≥50% of patients) are shown in **Table 3**.
- Most AEs were mild or moderate in intensity; 11 patients had severe AEs.
- CSF leaks occurred in 3 patients; these events were considered related to the surgical procedure and not to the gene therapy and resolved without consequence.
- No viral shedding was detected in any patient through 12 months after gene therapy.

Table 2. TEAEs experienced across all 3 trials

	Overall (N=28)
Number of TEAEs	563
Patients with ≥1 TEAE, n (%)	28 (100)
TEAE definitely related to treatment, n (%)	0 (0)
Deaths, n (%)	2 (7.1)

TEAE, treatment-emergent adverse event
[a]Deaths occurred 1 year and 5 years post-gene therapy and were considered unlikely to be related to treatment

Table 3. Summary of TEAEs (in ≥50% of patients)

Adverse event	1.8×10^{11} vg Dose (N=21), n (%)	2.4×10^{11} vg Dose (N=7), n (%)	Overall (N=28), n (%)
Pyrexia	20 (95.2)	7 (100.0)	27 (96.4)
Dyskinesia	21 (100.0)	3 (42.9)	24 (85.7)
Upper respiratory tract infection	14 (66.7)	6 (85.7)	20 (71.4)
Gastroenteritis	14 (66.7)	4 (57.1)	18 (64.3)
Pneumonia	16 (76.2)	2 (28.6)	18 (64.3)
Upper gastrointestinal haemorrhage	13 (61.9)	2 (28.6)	15 (53.6)

TEAE, treatment-emergent adverse event.

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Conclusions

These results indicate a pattern of steady and sustained reduction in OGC episodes after PTC-AADC gene therapy. Reducing OGC has the potential to improve quality of life for patients with AADC deficiency and their caregivers by decreasing clinical burden.

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