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Safety of Long-Term Treatment of Children with Ataxia-Telangiectasia (A-T) with Encapsulated Dexamethasone Sodium Phosphate (eDSP)

William P Whitehouse[1], Biljana Horn[2], Caralee Schaefer[2], Maureen Roden[2], Dirk Thye[2]
[1]University of Nottingham, Nottingham, U.K., [2]Quince Therapeutics, South San Francisco, CA

INTRODUCTION

- A-T is a rare neurodegenerative disorder manifesting with cerebellar ataxia, oculomotor apraxia, slurred speech, involuntary movements, telangiectasias, delayed growth and sexual maturation, sensitivity to ionizing radiation, immunodeficiencies, an increased risk of malignancy, and shortened survival.
- Encapsulation of dexamethasone sodium phosphate (DSP) in autologous erythrocytes is an investigational method of delivery of glucocorticoids which aims for sustained drug release with an improved safety profile.
- Monthly infusions of encapsulated DSP (eDSP) have been used as an investigational treatment for neuroinflammation in children with Ataxia-Telangiectasia in one Phase 2, one Phase 3, and an open label extension study.

OBJECTIVE

- The objective of this analysis is to describe the safety profile of long-term use of eDSP in children with A-T who received eDSP for a minimum of two years.

METHODS

- This was a post-hoc analysis of patients with A-T treated with eDSP in the Phase 3 ATTeST trial (NCT02770807; March 2017-May 2021) and in the ATTeST Open Label Extension (OLE) trial (NCT03563053; June 2018 - September 2022).
- Eligibility criteria included: age ≥ 6 years, weight >15 kg, ICARS walking score of 0-4, and absence of significant immunodeficiency or severe/unstable pulmonary, hepatic, renal disease, or uncontrolled diabetes. To continue into the OLE, participants were required to have completed 12 months in the double-blind ATTeST trial without serious or severe treatment-related adverse events or safety contraindications.
- Exposure duration was calculated from initiation of active treatment.
- Mean monthly eDSP doses were 8.2 mg (low-dose ATTeST), 17.4 mg (high-dose ATTeST), and 18.2 mg (OLE).
- Growth and laboratory safety outcomes, relevant to glucocorticoid-associated effects were evaluated.
- Height and weight were measured at study visits and converted to z-scores based on Center for Disease Control and Prevention and Indian Association of Pediatrics growth reference charts. Body mass index (BMI) was also calculated.
- Safety laboratory measures were followed longitudinally for up to 24 months, including hemoglobin, serum iron, random morning glucose, hemoglobin A1c (HbA1c), CD4+ cell count, and bone mineral density (BMD) z-scores.

RESULTS

- 68 participants were included (56% male, 44% female). The median age at enrollment was 9 years; 59% were in 6-9-year group and 41% in ≥ 10-year group.
- The mean duration of therapy was 39±11 months.
- Low serum iron was observed in 8/36 (22%) of participants at baseline and in 14/36 (39%) after 24 months of treatment.
- **Baseline** first-morning cortisol level of <138 nmol/L (<5µg/dL) was observed in 3 participants; one of these had a normal value on subsequent test. The other two low cortisol levels were not repeated, as they were not considered clinically relevant.

RESULTS

- 56 ad hoc cortisol levels were obtained in 42 participants during treatment; 3 resulted in values <138 nmol/L, and only one of these was a first-morning sample.
- No ACTH stimulation tests (indicated when adrenal insufficiency was clinically suspected) were required during the study.
- Bone mineral density z-scores changed from -0.47 (SD1.21) at baseline to -0.87 (SD1.25) at 24 months (N=37).

Table 1 Height and Weight z-scores

	Baseline	Month 24	Change from baseline
Height (cm) Height z-score	134 (SD17.5) -0.61 (SD1.37)	142.9 (SD15.2) -0.66(SD1.45)	8.9 (SD4.9) -0.06 (SD0.45)
Weight (kg) Weight z-score	31.26 (SD15.2) -0.8 (SD1.56)	38.1 (SD17.0) -0.75 (SD1.8)	6.8 (5.0) 0.04 (SD0.59)
BMI (kg/m^2) z-score	18.46 (SD3.38) -0.63 (SD1.42)	17.8 (SD4.45) -0.54 (SD1.54)	1.34 (1.95) 0.09 (SD0.82)

Table 2 Measured safety laboratory values at month 12 and 24

	Baseline	Month 24	Change from baseline
Hemoglobin (g/L) (N=62)	133 (SD14)	126 (SD11)	-7 (SD10)
Random morning glucose (mmol/L) (N=41)	5.23 (SD0.6)	5.27 (SD1.1)	0.036 (SD1.08)

	Baseline	Month 12	Change from baseline
HbA1c (%)	5.2 (SD0.29)	5.21 (SD0.22)	0.02% (SD0.21)
CD4+ (cells/µL) N=24)	400 (SD260)	394 (SD219)	-6 (SD107)

DISCUSSION

- **Growth –** Progressive growth faltering is characteristic in classic A-T, typically showing height z-scores between -1.0 to -1.5 in 6-9-year-olds (Natale, 2021). During treatment with eDSP, height and weight z-score stabilized, and no steroid-related linear growth suppression or weight increase were observed.
- **Hemoglobin and serum iron –** A modest decline in hemoglobin (-7 g/L) was seen over 24 months of eDSP treatment, without ongoing progressive loss after the initial 6 months. Monitoring for anemia and iron deficiency in pediatric recipients of eDSP remains important.
- **Glucose Metabolism and Adrenal Function –** No concerns related to glucose homeostasis or adrenal suppression were identified. Although routine monitoring is recommended, no confirmed cases of adrenal insufficiency occurred.
- **CD4+ counts -** Remained stable over the treatment period.
- **Bone mineral density –** Loss in bone mineral density is an expected feature of A-T, which complicates interpretation of treatment-related effects on bone health.

CONCLUSIONS

- Long-term treatment with eDSP in children with A-T was associated with stable growth and metabolic parameters without indications of steroid-related toxicities.

Disclosures: WPW is on a Scientific Advisory Board of Quince Therapeutics and has received consulting fees from Quince. BH. CS. MR and DT are employees of Quince Therapeutics and receive stock options as a part of their compensation.

Presented data can be downloaded at: https://doi.org/10.3389/fneur.2024.1526914.