Growth and Bone Mineral Density (BMD) in Children With Ataxia-Telangiectasia (A-T) Treated With Intra-Erythrocyte Dexamethasone (EryDex) for 24 months

Dirk Thye, Biljana Horn, Maureen Roden

Quince Therapeutics, South San Francisco, CA

ABSTRACT

Objective: Children with classical A-T have abnormal bone mineral density and growth. Their z-scores fall -2.5 standard deviations (SD) in height (Ht), and -1.5 SD in body mass index (BMI) by 16 years old, compared with unaffected children. Corticosteroids further adversely affect growth and bone health in children. We describe growth and BMD in children with A-T treated for ≥24 months with EryDex.

Methods: Patients receiving ≥24 months of EryDex, for treatment of neurological symptoms in the ATTeST and Open Label Extension (OLE) studies, are included in this report. Ht, weight (Wt) and BMI measurements were converted to z-scores using LSM calculations from CDC tables for subjects <20 years of age. Baseline and mean change from baseline (mCFB) after 24 months of therapy z-scores for Ht, Wt, BMI, and BMD ± SD are presented.

Results: Patients' characteristics (N=66) included: mean age (10.3±5.4 years); age <10 years (61%), 10-19 (34%), ≥20 (5%); male (56%), female (44%); genetic confirmation of A-T (97%); and mean alpha-fetoprotein level (266±223 ng/mL). Baseline mean±SD Ht z-score for 63 patients <20 years old, with available normative CDC data, was -0.73±1.38; 24-month mCFB -0.06±0.49. Baseline Wt z-score was -0.97±1.85; 24-month mCFB -0.02±0.71. Baseline BMI z-score was 0.75±1.70; 24-month mCFB 0.03±0.87. Baseline BMD z-score for 37 patients with available DEXA scans was -0.5±1.2 and mCFB at 24 months was -0.41±0.95.

Discussion: Over 24-month treatment with EryDex, minimal changes in z-scores for Ht, Wt and BMI (<0.1 SD) were observed, compared to baseline. These findings are encouraging, because the natural history study of classical A-T describes annual decline in Ht and BMI z-scores of -0.16 SD and -0.11 SD.[1] In untreated A-T patients, BMD z-scores are also known to decline over time.

Conclusions: 24 months of EryDex treatment did not adversely affect growth of children with A-T.

INTRODUCTION

- Ataxia-telangiectasia (A-T) is an inherited rare neurodegenerative and immunodeficiency disorder caused by mutations in the *ATM* gene
- Children with classical A-T have abnormal bone mineral density (BMD) and growth, and they experience height and weight faltering that continues throughout childhood and adolescence[1]
- Over time, median heights and weights decline to at or below the 3rd percentile on CDC charts (-1.88 z-score)[1]
- Previous short-term studies suggest that treatment with corticosteroids may lead to neurological improvements in patients with A-T[2-6]
- However, corticosteroids may further adversely affect growth and bone health in children
- EryDex is designed to provide continuous delivery of dexamethasone sodium phosphate from erythrocytes to patients who require prolonged use

OBJECTIVE

Describe growth and bone mineral density in patients with A-T treated for ≥24 months with EryDex

METHODS

EryDex System

- Autologous Intracellular Drug Encapsulation (AIDE) technology allows dexamethasone sodium phosphate to be encapsulated in autologous erythrocytes
- Components of the EryDex System:

1. **Red Cell Loader (Figure 1)**
   Non-invasive active medical device that automates the EryDex System (EDS) process and handles blood, drug, and processing solutions
2. **EryKit**
   Single-use, sterile, disposable kit includes bags and lines to contain blood, drug, and processing solutions

Figure 1. Red Cell Loader

EryDex System Process

Designed to be administered monthly at hospital or treatment center

Phase 1: Blood Collection
- 50 mL of patient blood is collected

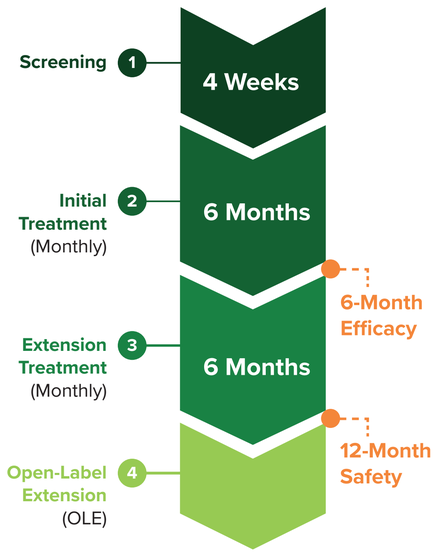
Phase 2: Blood Processing
- Red Cell Loader is set up by trained operator with EryKit and Process Solutions

Phase 3: EryDex Infusion
- EryDex (drug-loaded RBCs) are immediately (within 30 minutes) infused using a standard blood infusion set

RESULTS

- The ATTeST study (NCT02770807) is a phase 3, multicenter, randomized, double-blind, placebo-controlled trial to evaluate the effects of intra-erythrocyte dexamethasone sodium phosphate on neurological symptoms in patients with A-T[7]
- 175 ambulatory patients with A-T (aged ≥6 years; weight >15 kg) randomized (1:1:1) to receive monthly IV infusion of either:
  - EryDex ~5-10 mg (low dose)
  - EryDex ~14-22 mg (high dose)
  - Placebo
- At months 6 and 9, one-third of patients on placebo switched to active drug
- Treatment continued for 12 months, and at month 12 all eligible patients enrolled in the open-label extension (OLE) trial (NCT03563053)
- Changes in height, weight, body mass index (BMI), and bone mineral density (BMD) were evaluated in patients receiving ≥24 months of EryDex in the ATTeST and OLE trials

Figure 2. ATTeST Study Timeline



RESULTS

- The mean age of patients in this study was 10.3 ± 5.4 years of age, 61% of patients were under 10 years of age, and 97% of patients had genetic confirmation of A-T **(Table 1)**
- Over 24 months of treatment with EryDex, minimal changes in z-scores for height, weight, and BMI (<0.1 SD) were observed compared with baseline **(Table 2)**
- Weight gain typically associated with the use of steroids and steroid-derived products was not observed
- BMD z-scores declined over time, which is known to occur in untreated A-T patients

Table 1. Patient Characteristics

	EryDex (N=66)
Age (years)	10.3 ± 5.4
<10	61%
10-19	34%
≥20	5%
Male : Female (%)	55 : 44
Genetic confirmation of A-T	97%
Mean alpha-fetoprotein level (ng/mL)	266 ± 223

Table 2. Change in Height, Weight, BMI, and BMD

Z-scores	Baseline (N=63)	24-Month Change From Baseline
Height	-0.73 ± 1.38	-0.06 ± 0.49
Weight	-0.97 ± 1.85	-0.02 ± 0.71
BMI	-0.75 ± 1.70	0.03 ± 0.87
BMD	-0.50 ± 1.20	-0.41 ± 0.95

Data are mean ± SD

CONCLUSIONS

- Twenty-four months of EryDex treatment did not adversely affect the growth of patients with A-T
- The minimal changes seen in height, weight, and BMI are encouraging, because a natural history study of classical A-T describes declines in height and BMI z-scores of -0.16 SD and -0.11 SD per year, respectively[1]
- BMD z-scores declined over time, which is known to occur in untreated A-T patients
- Weight gain typically associated with the use of steroids and steroid-derived products was not observed

DISCLOSURES

This research was funded by EryDel and Quince Therapeutics. Dirk Thye, Biljana Horn, and Maureen Roden are employees of Quince Therapeutics.

References: 1. Natale VAI, Cole TJ, Rothblum-Oviatt C, et al. Growth in ataxia telangiectasia. *Orphanet J Rare Dis*. 2021;16(1):123. **2.** Buoni S, Zannolli R, Sorrentino L, Fois A. Betamethasone and improvement of neurological symptoms in ataxia-telangiectasia. *Arch Neurol*. 2006;63(10):1479-1482. **3.** Broccoletti T, Del Giudice E, Amorosi S, et al. Steroid-induced improvement of neurological signs in ataxia-telangiectasia patients. *Eur J Neurol*. 2008;15(3):223-228. **4.** Broccoletti T, Del Giudice E, Cirillo E, et al. Efficacy of very-low-dose betamethasone on neurological symptoms in ataxia-telangiectasia. *Eur J Neurol*. 2011;18(4):564-570. **5.** Zannolli R, Buoni S, Betti G, et al. A randomized trial of oral betamethasone to reduce ataxia symptoms in ataxia telangiectasia. *Mov Disord*. 2012;27(10):1312-1316. **6.** Hasegawa S, Kumada S, Tanuma N, et al. Long-term evaluation of low-dose betamethasone for ataxia telangiectasia. *Pediatr Neurol*. 2019;100:60-66. **7.** Zielen S, Crawford T, Benatti L, et al. Safety and efficacy of intra-erythrocyte dexamethasone sodium phosphate in children with ataxia telangiectasia (ATTeST): a multicentre, randomised, double-blind, placebo-controlled phase 3 trial. *Lancet Neurol*. 2024;23(9):871-882.