Cross-Sectional Analysis of International Cooperative Ataxia Rating Scale (ICARS) Subcomponent Scores in Children With Ataxia-Telangiectasia (A-T)

Dirk Thye, Biljana Horn, Maureen Roden

Quince Therapeutics, South San Francisco, CA

ABSTRACT

Objectives: Reliable measures of neurodegenerative disease progression over time are important for anticipatory guidance and assessment of treatment efficacy. The ICARS, developed for quantification of symptoms in cerebellar ataxia, was adopted in clinical trials for children with ataxia-telangiectasia as a research efficacy endpoint. Modified ICARS (mICARS), used in the ATTeST study, and Rescored mICARS (RmICARS) with condensed kinetic and oculomotor measures were also introduced as efficacy endpoints. The aim of this analysis is to describe baseline ICARS subcomponent scores by age in a cross-sectional analysis of treatment-naïve patients from ATTeST dataset, and to identify ICARS subcomponents that best reflect progression of disease by age.

Methods: Mean baseline ICARS scores ± SD were calculated for each of 7 age groups (age 6-12) for walking, standing, sitting, knee-tibia test, finger-nose test, pronation-supination, drawing, speech, and oculomotor subcomponents.

Results: The subcomponents of ICARS that showed disease progression with age and increased >25% between 6 and 10 years of age were: walking (3.3±1.58 to 6.6±2.55; 100% increase), standing capacities (8.7±3.35 to 12.2±2.77; 40% increase), and sitting (1.1±0.93 to 1.4±0.56, 27%increase). Scores in the kinetic function domain including drawing, speech, and oculomotor did not show age-related trends. No trends were identified in 11- and 12-year-olds in any of ICARS subcomponents, but the numbers of participants were small in these age groups.

Discussion: In this cross-sectional analysis, the posture and gait disturbance category of ICARS showed progression with age in untreated 6-10-year-old A-T children. Scores in the kinetic function category, comprising 52% of ICARS, showed no trends in progression over time, regardless of age. Scales with reduced kinetic function domain may be more sensitive than the full ICARS scores when assessing disease progression in younger children.

Conclusion: Additional data and new measures that correlate better with disease progression, particularly in older children with A-T, are needed.

INTRODUCTION

- Ataxia telangiectasia (A-T) is an inherited rare neurodegenerative and immunodeficiency disorder caused by mutations in the *ATM* gene
- Reliable measures of neurodegenerative disease progression over time are important for anticipatory guidance, and assessment of treatment efficacy
- The International Cooperative Ataxia Rating Scale (ICARS), developed for quantification of symptoms in cerebellar ataxia, was adopted in clinical trials for children with A-T as a research efficacy endpoint
- In 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 ataxia telangiectasia (ATTeST), modified ICARS (mICARS) and Rescored mICARS (RmICARS) with condensed kinetic and oculomotor measures were also introduced as efficacy endpoints[1]

OBJECTIVE

Describe baseline ICARS subcomponent scores by age in a cross-sectional analysis of treatment-naïve patients from ATTeST dataset, and to identify ICARS subcomponents that best reflect progression of disease by age

METHODS

Study Design

- 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[1]
- The ATTeST study included 175 patients with A-T (aged ≥ 6 years; weight >15 kg) and preserved walking capacity (ICARS score 0-4 for walking)
- ICARS was administered in its entirety, and mICARS and RmICARS were calculated from the documented ICARS scores
- For this cross-sectional analysis, total mean baseline ICARS, mICARS, and RmICARS scores were calculated for each of 7 age groups (ages 6-12)
- Mean baseline scores were calculated for each of 9 ICARS subcomponents (walking, standing, sitting, knee-tibia test, finger-nose test, pronation-supination, drawing, speech, and oculomotor subcomponents) in 7 age groups (ages 6-12)

ICARS and modified scales used to assess neurological symptoms

Full ICARS*

- **100 points, 19 items**
  - **Posture and gait disturbance** (34 points)
  - **Kinetic function** (52 points)
  - **Speech disorder** (8 points)
  - **Oculomotor disorders** (6 points)

*International Cooperative Ataxia Rating Scale.

mICARS†

- **54 points, 11 items**
  - **Posture and gait disturbance** (34 points)
  - **Kinetic function** (12 points)
  - **Speech disorder** (8 points)

†Modified International Cooperative Ataxia Rating Scale.

RmICARS‡

- **29 points, 9 items**
  - **Posture and gait disturbance** (23 points)
  - **Kinetic function** (2 points)
  - **Speech disorder** (4 points)

‡Rescored Modified International Cooperative Ataxia Rating Scale.

‡Note: RmICARS requested by the FDA.
Individual items are collapsed to better reflect clinical meaningfulness of changes.

RESULTS

Total ICARS and Modified Scales

- A total of 152 patients between 6 and 12 years of age were included in these analyses (older age groups were excluded due to small numbers of patients)
- The number of patients per age group was as follows: 6 years, n=9; 7 years, n=37; 8 years, n=23; 9 years, n=28; 10 years, n=32; 11 years, n=15; 12 years, n=8
- Total scores for ICARS, mICARS, and RmICARS increased between 6 and 10 years of age **(Figure 1)**
  - ICARS +19% from 6 to 10 years of age
  - mICARS +34% from 6 to 10 years of age
  - RmICARS +46% from 6 to 10 years of age
- The two ICARS-derived scales (mICARS and RmICARS) capture the subcomponents of ICARS with the fastest progression in 6- to 10-year-olds

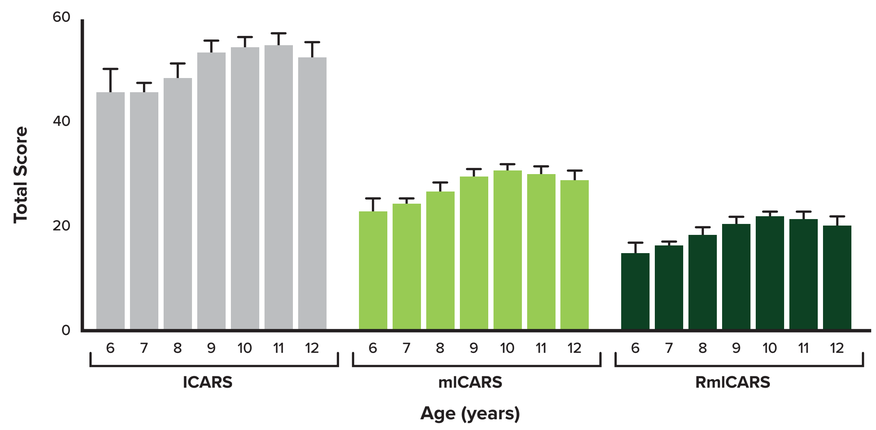

Figure 1. Mean Total ICARS, mICARS, and RmICARS Scores by Age

ICARS Subcomponent Scores

- The subcomponents of ICARS **(Figure 2)** that showed progression with age and increased >25% between 6 and 10 years of age were all in the posture and gait category:
  - Walking +100% from 6 to 10 years of age
  - Standing +40% from 6 to 10 years of age
  - Sitting +27% from 6 to 10 years of age
- Scores in the kinetic function, speech, and oculomotor domains did not show age-related trends
- No reliable trends were identified in 11- and 12-year-olds in any of the ICARS subcomponents, but the number of participants in these age groups was small

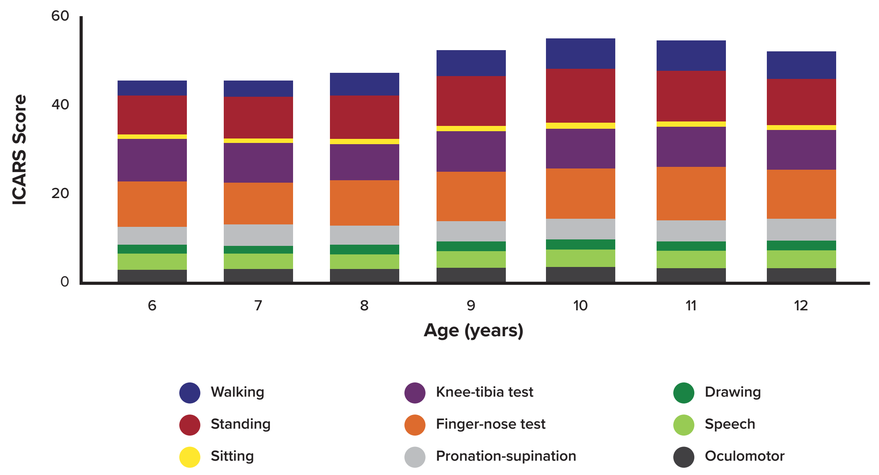

Figure 2. Mean ICARS Subcomponent Scores by Age

CONCLUSIONS

- We present ICARS scores from a large number of untreated patients with A-T between 6 and 12 years of age, who were selected based on walking capacity (ICARS walking score 0-4)
- The posture and gait category of ICARS showed progression with age in untreated patients with A-T between 6 and 10 years of age
- Scores in the kinetic function category, which comprises 52% of the total ICARS score, showed no trends in progression over time, regardless of age
- Scales with reduced kinetic function domain may be more sensitive than full ICARS scores when assessing disease progression over shorter periods of time in younger children
- Additional data and new measures that correlate better with A-T disease progression, in particular in older children as well as those not selected based on walking capacity are needed

DISCLOSURES

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

References: 1. 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.