A-TCRN | A-T Clinical Research Network

# The A-T Clinical Research Conference Zoom Session Summary
# Therapeutic Interventions for A-T: Part 1
# Thursday December 9th, 2021

## LAY SUMMARY OF EXISTING A-T RELATED TRIALS

### The Erydex Trial
**Guenter Janhofer, Chief Medical Officer, EryDel**

The 6-month ATTeST trial results of the EryDex system (red blood cells loaded with the steroid dexamethasone) were presented. The results after one year of treatment have been assessed **but are not yet published**, so the information presented is summarised but to maintain confidentiality we are not able to provide details. The results are likely to be published later in 2022.

ATTeST was an international placebo-controlled trial that took place at 22 clinical sites: 175 individuals with A-T were enrolled; however, somewhat fewer (164 participants) received treatment and only 107 received treatment according to the original trial protocol - this was due to difficulties attending hospital visits because of the COVID pandemic. Trial participants were treated with a high dose of EryDex, a low dose, or no drug (placebo).

Adverse side effects were carefully monitored but no consistent or reproducible events were observed, and there was no difference compared with the placebo control group.

The results showed positive findings in the group of 6–9-year-old participants who received the high dose of EryDex; demonstrating statistically significant improvement in the outcome measures used to monitor neurological symptoms.

**Future plans:**

Individuals with A-T who participated in the ATTeST trial are continuing to receive treatment in an open label extension (meaning that the participant knows that the treatment is being administered) and extended access programme. At the moment this treatment is not available to anyone who didn't participate in the trial.

Erydel's hope is to have US FDA market approval by the end of 2022 or early 2023. A team in the UK will also work with Erydel to discuss approval here.

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**N-acetyl-L- leucine (IB1001) Trial**
**Taylor Fields, Chief Product Development Officer, IntraBio**

N-acetyl leucine is a modified version of the amino acid, leucine. Amino acids are the building blocks of proteins which our bodies need to function properly.

IntraBio's N-acetyl-L-leucine (whose official drug name IB1001) has shown therapeutic benefits. However, "plain" or un-acetylated leucine has no similar therapeutic effect.

IB1001 is thought to enhance the function of the cell's powerhouses called mitochondria. There is also evidence that N-acetyl leucine can stabilise other cellular processes perhaps leading to decreased inflammatory signalling and possibly protect nerve cells against damage.

IB1001 has been used in trials of other rare neurological disorders, including Niemann Pick Disease type C (NPC) and GM2 Gangliosidosis. IB1001 treatment reduced ataxia in both NPC1 mice and GM2 mice. A trial in NPC patients showed significantly improved symptoms, functioning, and quality of life scores following treatment with IB1001. These improvements deteriorated when the drug was stopped.

Previously, 6 patients with A-T were assessed in a case series in Germany using the SARA ataxia rating scale to measure the severity of neurologic symptoms. Based on SARA scores, neurologic improvement was observed at 1 month of treatment in all patients.

IB1001, administered orally, is currently being used in an open label clinical trial for A-T. Confirmed individuals with A-T over 6 years of age, with SARA scores of 5-33, and the ability to walk with aid are eligible.

The new trial is underway with current recruitment at 5 study sites including the University of California, USA; Royal Papworth, UK; University of Giessen and Munich in Germany; and in Madrid, Spain. Currently, the trial has screened two thirds of the participants but has experienced COVID-related delays.

During the discussion, it was stressed that the precise function of IB1001 in the context of A-T is not yet fully understood but improved mitochondrial function and energy metabolism were strong possibilities.

IB1001 **will not treat the root cause of A-T**, but hopefully will provide symptomatic relief and offer a long-term neuroprotective effect. There was discussion that IB1001 could be used in combination with other therapies.



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## Nicotinamide Riboside (NR) Trial

**Stefanie Veenhuis, Paediatrician in training, Radboud University Medical Center, Nijmegen, the Netherlands**

Clinicians at the medical centre performed an open-label, proof-of-concept study that included 24 patients with A-T, all over 2 years of age and treated with nicotinamide riboside (NR) for 4 consecutive months. The trial was conducted between March and September 2019.

NR is a precursor of $NAD^+$, a component of the cell's system of energy metabolism. NR occurs naturally in fruit and can be taken as a dietary supplement. The Dutch trial was based on a preliminary study of A-T mice treated with NR where it was reported that the A-T mice showed improved neurological function and enhanced survival.

The human NR study included 18 people with classic A-T and 6 with variant or mild A-T. The dosage of NR was based on previous clinical studies using NR and was 25mg/kg/day with a maximum dose of 900 mg/day. Ataxia was monitored using various neurologic scales and a range of metabolomic laboratory measurements were also conducted. The neurologic scales showed significant improvement at 4 months treatment, but gains decreased when NR was stopped. These improvements were independent of age, type of A-T (mild or classic) and sex.

Results from the metabolomic study showed that levels of nicotinamide were normal in patients with A-T before treatment and increased during treatment with NR. Similarly, levels of a building block for DNA (the cell's genetic material) also increased.

Limitations of the study were discussed and agreed to be: 1) lack of a placebo control group 2) short study duration; and 3) no dose response analysis.

**Discussion points:**

1) An NR trial ongoing in Norway was also discussed. This trial involves 10 patients on NR for 2 years and 1 for 22 months. No side effects of NR were observed and there was a similar improvement in ataxia scores. This trial will end in March 2022.
2) A future trial with NR should include a placebo control-group and a longer duration of treatment. It would be beneficial to have a biochemical marker that improves with NR treatment.

## ASO Compassionate Use Trial

**Timothy Yu, Physician/Scientist, Boston Children's Hospital and Harvard Medical School**

Antisense oligonucleotides (ASOs) are short DNA or RNA sequences that have been used to target gene products. They are simple and inexpensive to manufacture and there is growing safety and efficacy data



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For A-T, ASOs have so far been used to alter patterns of abnormal splicing and ***improve expression of the A-T protein*****.**

However, ASOs are mutation specific, meaning that they **will not be suitable for all patients with A-T**. ASOs have been used for the treatment of Spinal Muscular Atrophy (SMA), where there is an approved therapy.

In May 2018, in collaboration with the A-T Children's Project and using the Global A-T Family Data Platform, three A-T mutations were evaluated for ASO treatment. In Jan 2020 a suitable patient (female, aged 2) was treated with the ASO (called atipeksen) by injection into the spine. The ASO appears to be well tolerated with no adverse effects. The patient is approaching an age (greater than 4 years old) where the impact of treatment can be assessed.

Using whole genome sequencing (WGS) data in the Platform, the number of A-T patients with mutations treatable by an ASO was evaluated. Of the 235 patients with WGS present in the Platform, 36 (15%) had a variant likely amenable to ASO therapy. This would require the development of 23 different ASOs. Interestingly, an A-T variant found in several patients in the UK may well be suitable for ASO therapy.

**Discussion points:**

1. Does administration of the ASO have to be through the cerebrospinal fluid? Systemic administration has not been tried but would require very high doses that would be difficult to get through FDA regulatory procedures.
2. Administration of the ASO involves 6 injections per year.



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