Circulating Sorbitol Levels and Severity of Disease in Patients with Sorbitol Dehydrogenase (SORD) Deficiency

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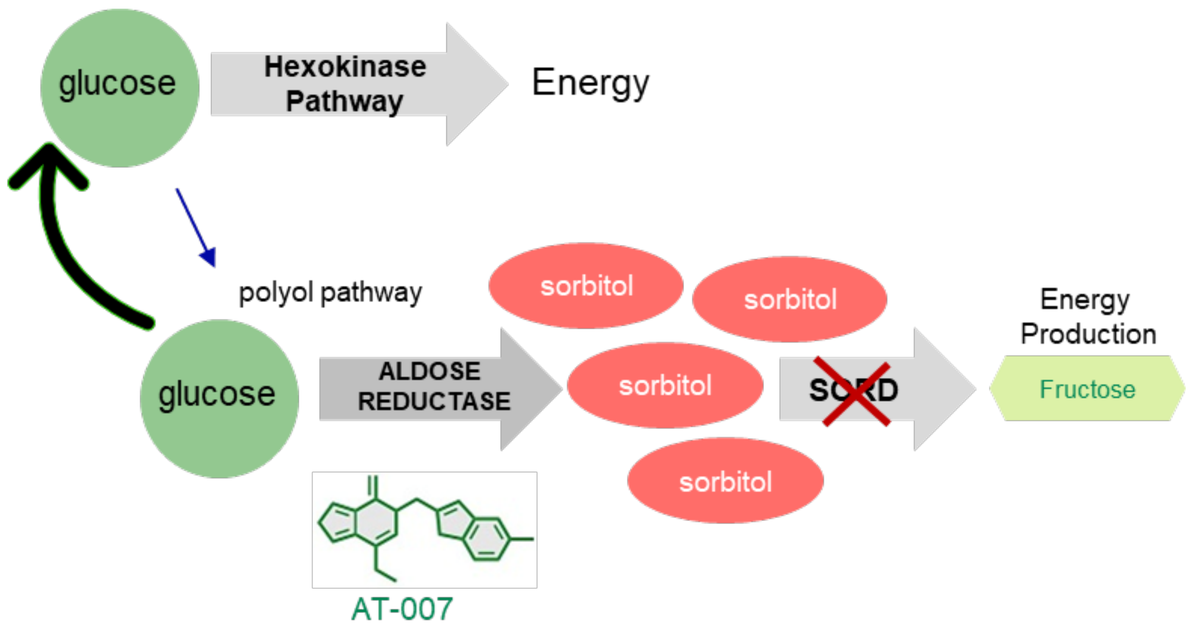
Introduction

- Sorbitol Dehydrogenase Deficiency (SORD Deficiency) is a rare, progressive, debilitating, hereditary neuropathy.[1,2]
- SORD Deficiency affects approximately 3,300 patients in the US and 4,000 patients in Europe.[1]
- Prior to the identification of the specific gene defect, patients with SORD Deficiency were classified symptomatically into the broader neurological diseases Charcot-Marie-Tooth Type 2 (CMT2) or distal Hereditary Motor Neuropathy (dHMN).[1]

SORD DEFICIENCY PATHOGENESIS

- SORD is the second enzyme in the two-step polyol pathway, an alternative glucose metabolism pathway.[1]
- Patients with SORD Deficiency are unable to process sorbitol, which leads to the accumulation of this toxic metabolite in the blood and tissues.[1]



- *In vitro* and *in vivo* studies have recently demonstrated that treatment with AT-007 prevents accumulation of sorbitol in a SORD-deficient animal model of disease and in cultured human fibroblasts from SORD Deficiency patients.[3]

Objectives

This qualitative report investigates the relationship between circulating blood sorbitol levels and the severity of disease

Methods

STUDY DESIGN

- The relationship between circulating blood sorbitol levels and the severity of disease was investigated in a cross-sectional cohort of patients who were diagnosed with SORD Deficiency and enrolled in an open-label pilot study evaluating safety, tolerability, pharmacokinetics and pharmacodynamic effects of AT-007.
- Clinical characteristics of disease and disease severity were collected through patient interviews, including age of onset of disease symptoms, severity of symptoms at the time of entry to the study, lower limb function, physical activity, use of leg braces or ambulatory assistance, gait and balance, involvement of upper limbs, presence of tremor.
- Sorbitol was measured by a validated LC-MS-MS assay and medical history was collected by patient interviews.

CLINICAL ASSESSMENT

- In order to determine whether circulating levels of sorbitol in the blood correlate with severity of disease, baseline sorbitol levels were examined alongside clinical vignettes describing each patient's age of onset, duration of disease, and current functional status. They were broken in to three clusters.
  - The first cluster analyzed a group of 3 patients in their early 20s with ~10 years of disease history
  - The second cluster analyzed 2 patients around 30 years of age with ~15-20 years of disease history
  - The third cluster analyzed patients over 40 years of age with >20 years of disease history

Disclosures

This research was funded by Applied Therapeutics Inc.

Results

BASELINE SORBITOL LEVEL AND DISEASE SEVERITY

Patient	Age	Sorbitol Level (ng/mL)	Leg Braces?	Climbs Stairs Independently?	Upper Limb Involvement/Tremor?
1	23	~45,000	Yes	No	Yes
2	32	~45,000	Yes	No	Yes
3	20	~35,000	No	Yes	No
4	42	~30,000	No	Yes	No
5	19	~30,000	No	Yes	No
6	41	~40,000	Yes	Yes	No
7	54	~45,000	Yes	No	Yes
8	28	~25,000	No	Yes	No

CLINICAL SUMMARIES

CLUSTER 1 (Patients in early 20s with ~10 years disease history)

- **Patient 5:** Patient experiences lower limb symptoms which have not significantly impacted ambulation but has impacted performance in sports. Symptoms are limited to the lower limbs, and she can still climb stairs albeit slower than her peers. Her sorbitol level is ~30,000 ng/mL.
- **Patient 3:** Clinical presentation of of symptoms is largely limited to the lower limbs. He walks slowly and is prone to falls. He has difficulty with balance and gait occasionally leading to falls. He has limited physical activity and does not play sports anymore. His sorbitol level is ~35,000 ng/mL.
- **Patient 1:** Patient has significant gait, balance, and stability issues as well as lower limb muscle atrophy. He can not walk without leg braces and can not stand more than a few minutes. Additionally, he has hand tremor and describes his activity as severely limited. He has one of the highest sorbitol levels in the cohort at ~45,000 ng/mL.

CLUSTER 2 (Patients ~30 years old with 15-20 years disease history)

- **Patient 8:** Patient has balance and gait problems as well as foot drop and must wear sturdy, flat shoes. She is still very active, walking several miles per day and enjoys hiking. She can climb stairs independently but worries about balance and falls. Her sorbitol level is ~25,000 ng/mL.
- **Patient 2:** Patient has significant balance and stability issues as well as decreased lower limb function. He can't walk up the stairs unless he pulls himself up using the handrail. He has difficulty walking uphill and downhill as well as walking on uneven surfaces. His physician has recommended leg braces but patient refuses to wear them. In addition, he has hand tremor, which he notices worsening over time. His sorbitol level is ~45,000 ng/mL.

CLUSTER 3 (Patients over 40 with >20 years disease history)

- **Patient 6:** Patient has significant lower limb muscle atrophy and maintains physical activity through walking and biking but with significant difficulty. Additionally, he has potential sensory loss and feels no pain in his lower limbs even when he should. His sorbitol level is ~40,000 ng/mL.
- **Patient 4:** Patient primarily suffers with balance issues and needs to move slowly to prevent slipping due to lack of stability. She is physically active doing CrossFit and yoga multiple days a week but has started having difficulty lifting legs and with dorsiflexion. She feels unstable on stairs but is able to climb stairs unassisted. Her sorbitol level is ~30,000 ng/mL.
- **Patient 7:** Patient is severely compromised from a mobility and motility, poor ambulation, and requires the use of a walker or wheelchair. She is unable to engage in physical activities and has significant joint pain and neuropathic pain. She is unable to climb stairs and requires a chair lift. Her sorbitol level is ~45,000 ng/mL.

Conclusions and future directions

- A high level of sorbitol (>40,000 ng/mL) was associated with greater lower limb deficits and eventual loss of mobility and ambulation deficit, more significant balance problems, and upper limb neuropathy and tremor.
- Qualitative analysis suggests that patients with a higher level of sorbitol have a more severe prognosis.
- An ongoing placebo-controlled Phase 2/3 study is evaluating the effect of AT-007 on sorbitol reduction and clinical outcomes in SORD Deficient patients.

Acknowledgements

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References

1. Cortese A, et al. Nat Genet 2020;52:473–481.
2. Lassuthova P et al. Sc Reports 2021; 11:8443
3. Oral presentation Peripheral Nerve Society Annual meeting 2021: Pre-Clinical Treatment Studies of SORD Neuropathy with Novel Aldose Reductase Inhibitor (Rebelo et al).