ABSTRACT

Background: Individuals with Adult Tay-Sachs Disease (ATSD) develop clinical symptoms by early teenage years and lose ability to walk. No therapy has yet been shown clinically effective. ATSD is caused by the absence of GM2 gangliosidase activity and GM2 ganglioside accumulation in neuronal lysosomes. The most prevalent ATSD mutation, e2695, is not believed to impact HexA enzyme function but instead causes post-translational misfolding and reduced enzyme stability. Others have shown in vitro that pyr in mammalian (PYR) (200mg, tid), and acetylcysteine (10 ml, bid) were continued without change. Weekly Hex enzyme assays and monthly hematologic tests (CBC) were conducted. The 75 mg QD was again initiated after being off PYR for eight weeks.

CASE STUDY RESULTS

Results: No noticeable side effects were observed during the four weeks of treatment. Additional follow-up and comparisons to the modeled response will be presented.

MODEL OVERVIEW

No animal models of ATSD exist. The use of pyrimethamine (PYR) as a potential pharmacological chaperone therapy for ATSD patients was therefore simulated using in silico models. Simulations were based on three computer models. The models used 19 differential equations solved with the MATLAB ode45 function.

PHARMACOKINETIC MODEL

The PK model is based on published studies at Ref 6, with repeat measurements taken on 14 normal adults (60 to 86 kg) each taking a single dose of 25 mg PYR (mean ± SD):

- Elimination half-life (0.5 ± 0.3 days)
- Time to max concentration (4.2 ± 2.7 hr)
- Area under curve (15.1 ± 5.5 mg*h/L)
- Volume of central compartment (75.8 ± 26.6 L)

Model 1: Classical Two Compartment PK Model

PK Model Results

Figure 1. [PYR] simulated doses of 75 mg QD for two weeks. Time to reach steady state (~2 wks), steady state plasma concentrations, and half-life (t1/2) matched published studies (Ref 6). The CISP:Plasma ratio is modeled at 20% (for reference only).

CELLULAR MODELS

Model 1: Endoplasmic Reticulum

Model 2: Lysosomes

Model 3: GM2 Storage

Model Simulation Results

Figure 2. Simulated ATSD Patient – Shown are the results from the model simulations of an ATSD patient (i.e., translation rates of 0.1, k1 = 0.1, and degradation rates set to the same value). The timelines were run with different PK parameters (0.25, 25, 75, and 150 mg QD) given continuously for 100 days. The initial values are the steady state values obtained from a two-year simulation with no PYR dose. (A) Simulation of mutated HexA (ΔGlu27) concentration in lysosomes. (B) Simulation of lysosomal HexA (ΔGlu27) and HexB (ΔGlu27) concentration in lysosomes. (C) Simulation of GM2 storage (storage) and HexB (ΔGlu27) concentration in lysosomes. (D) Simulation of GM2-GM2 activator complex.

MODEL LIMITATIONS

If this represents the normal enzyme concentration, then the normal enzyme concentration is 25 μM.

- The models used repeated parallel calculations of 19 ordinary differential equations for each simulated trial to estimate the molecular concentrations in each compartment. As an example, the calculation for HexA concentration in each compartment is shown below. The equation accounts for the degradation of GM2-GM2 activator complex (ΔGlu27) concentration:

\[ \frac{dGM2}{dt} = \frac{-GM2}{t_1/2} \]

where:

- t1/2 = half-life (t1/2) = 18.0 mg GM2

The model incorporated an algorithm by which HexA is stabilized by both PYR and GM2. With this, reductions in GM2 could also decrease the effective half-life of ATSD HexA and thereby limit chaperone therapy effectiveness.

- Observation of clinical improvements in long-term studies or in proven CNS neuronal biomarkers of HexA or GM2 are required to establish PYR efficacy.

REFERENCES

2. Conzelmann E and Sandhoff K, Partial Enzyme Deficiencies: Residual GM2 activator protein is based on GM2 concentration within normal brain tissue at 20 nmol/g wet weight of tissue (Ref 6), half-life for normal fibroblasts at 78 hrs (Ref 7), and all degradation occurring in lysosomes.
3. Enzyme activity are shown comparing the average for blood samples taken after being on PYR at 75 mg/day for at least three weeks (“ON”) to the average of the samples taken when no PYR was taken for at least the previous three weeks (“OFF”). The basal values used in the analysis in Figure 4 are shown with a green (“OFF”) and blue (“ON”) circles.

Figure 3. Blood samples were analyzed weekly (Thomas Jefferson University) except following the initiation of the study and at the end after the final dosing period. Based on the pharmacokinetic and cellular models, it was hypothesized that the response to initiation or termination of the PYR would require approximately three weeks. The HexA values used in the analysis for Figure 4 are shown with a green (“OFF”) and blue (“ON”) circles.

Figure 4. Enzyme activity are shown comparing the average for blood samples taken after being on PYR at 75 mg/day for at least three weeks (“ON”) to the average of the samples taken when no PYR was taken for at least the previous three weeks (“OFF”). The basal values used in the analysis for Figure 4 are shown with a green (“OFF”) and blue (“ON”) circles.