One Year Follow-up on Chaperone Therapy for Two Siblings with Adult Tay-Sachs Disease

John G. (Jack) Keimel, University of Minnesota and New Hope Research Foundation, Minnesota

Background: Adult Tay-Sachs Disease (ATSD) is caused by inadequate β-hexosaminidase-A (HexA) activity resulting in GM2 ganglioside accumulation. Individuals with ATSD develop ataxia and dystarhythmia by early teenage years and later lose ability to walk. No therapy has yet been shown clinically effective. The most prevalent ATSD mutation, og269S5, does not impact HexA enzyme function but rather causes post-translation misfolding and reduced enzyme stability. In-vitro studies have demonstrated that pyrrolimethamine (PYR) improves og269S5 mutated HexA stability and transport to lysosomes. (Ref 1)

Case Report: Two brothers confirmed with ATSD and the og269S5 mutation had been taking a substrate reduction therapy, miglustat (200mg, tid), for >4 years, but at age 24 and 25 years, showed accelerated decline in coordination and leg muscle strength resulting in inability to rise unassisted from a sitting position or climb stairs. PYR (75mg qd) at dinner was begun in combination with folic acid (5mg, qd). Repeat leukocyte HexA assays and hematologic tests (CBC) were conducted. A prior short-term case study of the older brother reported leukocyte HexA activity increased (~3x) for up to 8 weeks following start of daily PYR. (Ref 2)

Results: Additional follow-up on the older brother showed decline in leukocyte HexA to baseline values after 13 weeks. The younger brother also showed an increase (~2x) in leukocyte HexA activity, but repeatedly encountered anorexia and vomiting after being on PYR for >4 weeks. Hematologic results remained normal for both. PYR (75mg, qd) was subsequently cycled 3 weeks ON followed by 3 weeks OFF for both siblings. Additional follow-up results are presented.

Pyrimethamine (PYR) was selected as a potential pharmacological chaperone drug for ADTS patients based on prior cellular studies showing improved stability of og269S5 mutated HexA and increased transport to the lysosomes. (Ref 1) A dosage of 75 mg qd was based on the pharmacokinetic model (below) and selected to achieve a steadystate "periphery" PYR concentration of 10 μM. PYR was given in combination with folic acid (5mg qd) to offset partial dihydrofolate reductase inhibition reported to be caused by PYR.

Pharmacokinetic Model: The PK model is based on the Weidekamm et al study (Ref 3) with repeat measurements taken on 14 normal adults (60 to 85 y/o) each taking a single dose of 25 mg PYR (mean ± SD):

- Elimination half life (95.5 ± 30.8 hr)
- Time to max concentration (4.2 ± 2.7 hr)
- Area under curve (19.1 ± 5.6 mg/hr/L)
- Volume of central compartment (75.9 ± 28.6 L)

Classical Two Compartment PK Model:

<table>
<thead>
<tr>
<th>Daily PYR Oral Dose</th>
<th>Gl</th>
<th>Derived First Order Rate Constants</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>k21</td>
<td>ka</td>
</tr>
<tr>
<td>Periphery</td>
<td>k12</td>
<td>k21, 0.065/hr</td>
</tr>
<tr>
<td>Plasma</td>
<td>1</td>
<td>k12, 0.071/hr</td>
</tr>
<tr>
<td></td>
<td></td>
<td>k21, 0.065/hr</td>
</tr>
<tr>
<td></td>
<td></td>
<td>k12, 0.016/hr</td>
</tr>
</tbody>
</table>

PK Model Results:

- Plasma
- Periphery
- CSF

![Graph](image)

Figure 1. (PYR) simulated dose of 75 mg QD for two weeks. Time to steady state (~2 wks), steady state plasma concentration, and half-life (68 hrs) match published studies (Ref 3 & 4). The CSF/Plasma ratio is modeled at 20% (for reference only).

Drug Regimen: PYR 25mg qd was begun for 2 weeks followed by 75mg qd for 8 weeks and then stopped to verify baseline HexA levels. PYR was again stopped in week 36 after observing a downturn in HexA level. PYR (75mg, qd) was subsequently cycled 3 weeks ON followed by 3 weeks OFF. Miglustat (200mg, tid) was stopped at week 46. Psychiatric medications were managed on the follow-up period as deemed appropriate by the patient’s psychiatrist.

Drug Regimen: PYR 75mg qd started at week 19 and stopped at week 31 after exhibiting anorexia and severe vomiting. The illness resolved within 4 days. PYR 75 mg qd was started again at week 36 but terminated at week 42 after again showing the same condition. PYR (75mg, qd) was subsequently cycled 3 weeks ON followed by 3 weeks OFF. Miglustat was stopped at week 45.

RESULTS SUMMARY

- HexA activity towards 4-methylumbelliferyl N-acetylglucosamine 6-sulfate (MUGS) increased when PYR (75 mg qd) was taken for more than 3 weeks ("ON") compared to when no PYR had been taken for at least 3 weeks ("OFF")
- HexA levels ON PYR declined for both siblings between week 34 (May 12, 2009) and week 56 (Oct 13, 2009).
- Other observations made following the initiation of PYR medication and throughout the remaining course of follow-up are below:
  - Neither sibling had significant changes in physical ability or coordination.
  - Neither sibling had a major psychiatric event requiring hospitalization.
  - The younger brother exhibited anorexia and vomiting after taking PYR (75 mg qd) for 6 to 8 weeks. Illness resolved within 4 days of discontinuing PYR. No other side effects were observed.
  - Marginally low % lymphocyte levels were measured in both siblings at baseline and throughout the follow-up period. Other blood cell count differentials and serum folic acid remained within the normal range.

REFERENCES

2. Keim J, Charnas L. Case report of chaperone therapy for Adult Tay-Sachs Disease and comparison to an in-silico pharmacokinetic and cellular simulation. Lysosomal Disease Network WORLD Conference, Feb 2009

DISCUSSION TOPICS

- The HexA og269S5 protein is known to be unstable with a short half-life (Ref 5). Measurement of this enzyme level may require special processes and handling to obtain reliable results. Warm temperatures or delays during transport may affect measurement of this HexA. See Figure 5.
- While it has been hypothesized that increasing enzyme levels to 100% of normal may be sufficient to prevent ganglioside storage (Ref 6), an in-silico model has projected a possible long-term decline in HexA activity accompanying an effective chaperone therapy (Ref 2).
- While lack of additional significant decline in physical ability or coordination is encouraging for these two siblings, a biomarker specific to ganglioside storage levels within the CNS would be helpful in assessing efficacy and optimizing dose.
- Long-term clinical studies are required to establish PYR efficacy.