Adjunctive Sertraline for the Treatment of HIV-Associated Cryptococcal Meningitis
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Abstract

Introduction: Mortality from HIV-associated cryptococcal meningitis (CM) remains unacceptably high. Identifying new effective antifungals is of paramount importance. We evaluated the efficacy of adjunctive sertraline, previously demonstrated to be active against Cryptococcus neoformans both in vitro and in murine models.

Methods: 173 HIV-infected persons with CM were prospectively enrolled in a phase II/III, open-label clinical trial in Kampala, Uganda between August 2013 and October 2014. Sertraline at doses of 100–400 mg/day was added to standard therapy (amphotericin B + fluconazole 800 mg/day). Early fungicidal activity (EFA) was measured as the rate of cryptococcal clearance in serial quantitative CF cultures and was validated by mixed effect model for all participants with at least one sample of CFM and at least 2 CF cultures (N=128). Sertraline concentrations in plasma were measured using high-performance liquid chromatography–mass spectrometry (HPLC–MS) and 80 subjects were evaluated to see how rapidly sertraline achieves steady state.

Results: There were no deaths in subjects with sertraline 27% faster rate of clearance compared with recipients of standard care: EFA = 0.38 vs. 0.50 for those with vs. without sertraline (p<0.05). Sertraline reached steady state in plasma by day 7, with a mean level of 242 (95%CI: 184–302) ng/mL at 400 mg/day and 411 (329–493) ng/mL at 400 mg/day. Plasma levels reached 72% of steady state levels by day 3. The projected steady state brain tissue concentration at 200mg/day was a mean of 3.9 (95%CI: 2.9–4.8) mcg/mL, and at 400 mg/day was 6.6 (5.3–7.3) mcg/mL. Among isolates, the MIC was 0 mcg/mL for 9%, ≤ 0.5 mcg/mL for 29%, 0.5–4 mcg/mL for 85%, and 8–50 mcg/mL for 9% of isolates. In vitro synergy studies (n=9) found a median 2-fold reduction in the MIC with a combination of sertraline and fluconazole. For sertraline at doses 200–400 mg/day, the incidence of paradoxical IRIS or relapse or death was 12.2%.

Conclusions: Sertraline provides additional activity against Cryptococcus with improvements in CSF clearance rates and appears to reach therapeutic levels in vivo. This phase II trial of oral medication (0.05 mg/kg) provides a promising Adjunct for CM when added to standard antifungal therapy. This pilot study justifies a larger randomized trial to elucidate if sertraline has a survival benefit for the treatment of cryptococcal meningitis.

Method

1. 173 HIV-infected patients diagnosed with cryptococcal meningitis in Kampala, Uganda received standard therapy + adjunctive sertraline.
2. Participants received increased doses (100–400mg/day) for sertraline for 14 days (Table 1), followed by oral placebo medication (0.05 mg/kg) per day for 45 days.
3. Standard therapy included amphotericin B (0.7–1.7 mg/kg/day) for 7–14 days + fluconazole (400–1200mg/day induction followed by 400mg/day consolidation).
4. CSF from serial therapeutic-lymphatic punctures had quantitative cultures, which were used to calculate the rate of CSF clearance via mixed effect models.
5. Results: In all participants who had culture-positive, first episodes of CM with at least 2 quantitative cultures (N=128; Figure 1).

Secondary outcome measures included:
- In-vitro MIC testing of sertraline isolates (N=91).
- Sertraline concentrations in plasma over a 4-week sampling period (N=777).
- Incidence of CNS IRIS and Cryptococcal relapse.
- MIC assays were performed on sertraline using RPMI 1640 media according to Clinical Laboratory Standards Institute M27-A3 protocol.
- MIC was defined as the concentration at which growth was 100% inhibited.
- Additional-sertraline-fluconazole MIC synergy assays were performed on a subset of histological isolates (COAT Trial, ClinicalTrials.gov NCT01751512).
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- Brain concentrations of sertraline were predicted based on a previous analysis of standard plasma concentrations.
- There was a median 16-fold increase in brain compared to plasma concentrations.

Table 1: Clinical presentation and outcomes by daily sertraline dose

<table>
<thead>
<tr>
<th>Dose (mg/day)</th>
<th>N</th>
<th>Positive sertraline</th>
<th>No sertraline</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>150</td>
<td>11</td>
<td>7 (64%)</td>
<td>4 (36%)</td>
<td>0.039</td>
</tr>
<tr>
<td>200</td>
<td>59</td>
<td>35 (59%)</td>
<td>24 (41%)</td>
<td>0.008</td>
</tr>
<tr>
<td>300</td>
<td>46</td>
<td>28 (61%)</td>
<td>18 (39%)</td>
<td>0.003</td>
</tr>
<tr>
<td>400</td>
<td>26</td>
<td>16 (62%)</td>
<td>10 (38%)</td>
<td>0.011</td>
</tr>
</tbody>
</table>

Figure 1: Analysis cohort: the primary outcome of EFA was measured in all participants with first episode of culture-positive CM and 32 quantitative cultures. Secondary outcomes included in vitro susceptibility testing of Cryptococcus isolates (MIC testing) and sertraline plasma concentrations of sertraline by HPLC Mass Spectrometry.

Results

- Early mortality from HIV-associated CM remains unacceptably high, in large part due to the high cost, toxicity, and limited repertoires of effective antifungals.
- There is a critical need for new effective antifungals that are accessible in resource-limited settings.
- The commonly used selective serotonin reuptake inhibitor (SSRI) antidepressant sertraline (Zoloft) is an in vitro antagonist to Cryptococcus.
- Sertraline is concentrated into the brain (16-fold over plasma).
- We conducted a phase IIb clinical trial to test if adding sertraline to standard antifungal therapy would result in improved CSF fungal clearance from CSF.

Table 2: Sertraline MIC for Cryptococcal clinical isolates. The majority of isolates tested had MIC ≤ 4 mcg/mL, suggesting that sertraline is a potent inhibitor of Ugandan Cryptococcal isolates.

<table>
<thead>
<tr>
<th>Sertraline MIC (mcg/mL)</th>
<th>N</th>
<th>%</th>
<th>Cumulative %</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 4 mcg/mL</td>
<td>100</td>
<td>83</td>
<td>83</td>
</tr>
<tr>
<td>3–4 mcg/mL</td>
<td>10</td>
<td>5</td>
<td>88</td>
</tr>
<tr>
<td>2–3 mcg/mL</td>
<td>4</td>
<td>2</td>
<td>90</td>
</tr>
<tr>
<td>1–2 mcg/mL</td>
<td>2</td>
<td>1</td>
<td>91</td>
</tr>
<tr>
<td>&gt;2 mcg/mL</td>
<td>2</td>
<td>1</td>
<td>92</td>
</tr>
</tbody>
</table>

- In vitro susceptibility testing results were similar to previous studies using reference strains and historical isolates from previous Ugandan cohorts (unpublished data) with sertraline MIs in the range of 4-6 mcg/mL.
- Sertraline was observed a trend towards improved CSF efficacy by isolate MIC (Figure 3). Synergy testing on 9 COAT trial isolates suggests an additive effect of fluconazole on sertraline MIC and vice versa (Table 3).
- Based on results of pharmacokinetic assays at therapeutic doses of 400mg daily (Figure 4), steady-state sertraline levels are predicted to exceed the MIC for Cryptococcus in the CNS.

Conclusions

- Adjunctive sertraline provided improved CSF rate of clearance compared to historical controls receiving standard therapy alone.
- In vivo, sertraline is active against Cryptococcus and is synergistic with fluconazole.
- At therapeutic doses of 400mg daily, sertraline concentrations are predicted to rapidly exceed the MIC for Cryptococcus.
- Possible unforeseen benefits of adjunctive sertraline may be decreased incidence of cryptococcal relapse and paradoxical IRIS.
- Sertraline is promising adjunct to standard antifungal therapy.
- The ASTRO-CM randomized clinical trial will test if sertraline has a survival benefit, starting in February 2015.

References and Acknowledgments

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