Safety and Pharmacokinetics of Solithromycin in Subjects with Hepatic Impairment

ECCMID 2014 – P1686

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Objectives: To evaluate the safety, pharmacokinetics (PK), and protein binding of solithromycin in subjects with mild, moderate and severe hepatic impairment compared to healthy subjects with normal hepatic function (matched for age, weight, and gender).

Methods: This was a Phase 1, open-label, multiple-dose study in subjects with mild (Child-Pugh Class A), moderate (Child-Pugh Class B), and severe (Child-Pugh Class C) hepatic impairment and healthy matched control subjects with normal hepatic function. All subjects received a once-daily dose of 800 mg on Day 1 followed by 400 mg on Days 2 through 5.

Results: 33 subjects were enrolled: 8 with mild impairment (mean Child-Pugh score 5.625), 8 with moderate impairment (mean Child-Pugh score 7.375), 8 with severe impairment (mean Child-Pugh score 10.625), and 9 healthy controls with normal hepatic function. One subject, a healthy control, discontinued study drug after 2 doses due to a rash; all other subjects (n=32) completed the study. Overall, the number of subjects reporting treatment-emergent AEs in the hepatic impaired cohorts (mild n=1, moderate n=4, severe n=4) was no greater than in the control group (n=4). The most commonly reported AEs were mild diarrhea and mild headache. After 5 days of solithromycin administration, mean changes from baseline in liver function tests on Day 8 were not clinically significant in any cohort and did not differ significantly between cohorts. For ALT (IU/L), mean (±SD) changes by cohort: control = 2.6±4.47, mild = 4.0±8.00, moderate = 7.8±6.92, severe = 6.3±14.61. For AST (IU/L), mean (±SD) changes by cohort: control = -0.6±2.92, mild = 0.4±5.93, moderate = 0.1±10.56, severe = 5.8±22.44. For direct bilirubin (mg/dL), mean (±SD) changes by cohort: control = 0.00±0.053, mild = 0.00±0.076, moderate = 0.03±0.046, severe = 0.04±0.207. No individual change from baseline in any liver function test was considered clinically significant. PK parameters on Day 5 were compared between the hepatic impaired cohorts and the control group, and geometric mean ratios were calculated (see Table).

Comparison	Parameter	Test Group	Reference Group	Geometric Mean Ratio (%) (test/reference)	90% Confidence Intervals
Mild versus Control	Cmax(ng/mL)	785.957	649.126	121.08	64.38 - 227.71
	AUC0-t(ng*hr/mL)	8872.658	7554.940	117.44	56.64 - 243.50
	AUC0-tau(ng*hr/mL)	7900.103	10491.88	75.30	47.89 - 118.39
Moderate versus Control	Cmax(ng/mL)	683.897	649.126	105.36	56.02 - 198.14
	AUC0-t(ng*hr/mL)	8902.279	7554.940	117.83	56.83 - 244.31
	AUC0-tau(ng*hr/mL)	7509.789	10491.88	71.58	45.52 - 112.55
Severe versus Control	Cmax(ng/mL)	504.311	649.126	77.69	41.31 - 146.11
	AUC0-t(ng*hr/mL)	8306.315	7554.940	109.95	53.03 - 227.95
	AUC0-tau(ng*hr/mL)	6175.788	10491.88	58.86	37.44 - 92.55

No accumulation was noted in any of the hepatic impaired cohorts on Day 5, though an increased half-life (h) was observed in the severe group (control = 8.9, mild = 10.2, moderate = 10.4, severe = 15.7). The mean plasma protein binding percentage, at Day 5 C_{max}, was not significantly affected by mild or moderate hepatic impairment, but was slightly lower in the severe cohort.

Conclusions: Macrolide antibiotics, like solithromycin, are primarily metabolized and excreted through liver-dependent mechanisms; this study evaluated the safety and PK of solithromycin in patients with chronic liver disease. No dosage adjustment is needed when administering solithromycin to patients with mild, moderate, or severe hepatic impairment. Solithromycin was well tolerated in this patient population and no significant differences in safety, compared to healthy controls, were noted.