Liver-Targeting Prodrug (LTP) Technology Offers Opportunity of New Generation Lipid Lowering Agents

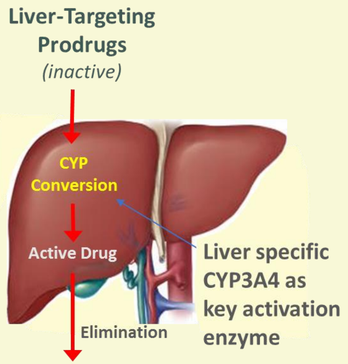
TAP TO GO BACK TO KIOSK MENU

Lin Zhi, Eric G. Vajda, and Keith B. Marschke

Ligand Pharmaceuticals Inc., 3911 Sorrento Valley Boulevard, Suite 110, San Diego, CA 92121

INTRODUCTION

LTP Technology™



- Statin intolerance has been a challenge for a subset, but still large number, of patients with dyslipidemia. Strategies have been attempted to increase statin liver selectivity to reduce drug exposure outside the liver. We report that the LTP technology, developed to enhance liver selectivity of small molecule therapeutic agents, significantly improves liver targeting of rosuvastatin in a rat model. LTP compounds are converted by enzyme CYP3A4, expressed primarily in the liver, to an active form leading to higher liver concentrations of the active drug.
- Rosuvastatin and 6 LTP analogs were orally administered to Sprague-Dawley rats (3/group) at the same 5 mg/kg doses. Blood was sampled from jugular and hepatic portal veins (HPV), and liver tissue was harvested and snap-frozen in liquid nitrogen at 1 and 5 hours post dosing. Compound concentrations were measured by LC-MS/MS.

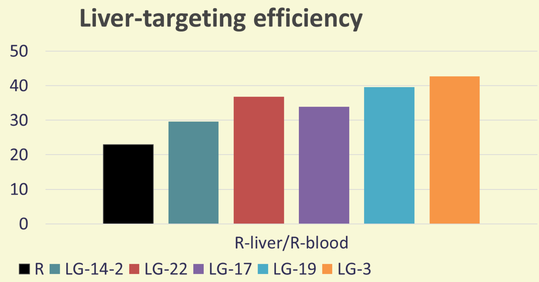
Prodrug (P) and Rosuvastatin (R) in Blood (B) and Liver (L) 1 hour After Oral Dosing

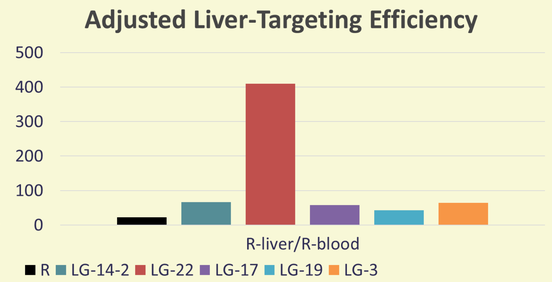
Compound	R	LG-23	LG-14-2	LG-22	LG-17	LG-19	LG-3
R_L (nmol/g)	**1.95 ± 1.16**	**35.8 ± 11.9**	**24.9 ± 2.4**	**20.8 ± 4.9**	**12.5 ± 2.7**	**5.16 ± 2.85**	**2.68 ± 0.34**
R_B (nmol/mL)	0.085 ± 0.064	1.51 ± 0.60	0.84 ± 0.10	0.56 ± 0.23	0.37 ± 0.08	0.13 ± 0.09	0.063 ± 0.014
R_{HPV} (nmol/mL)	0.89 ± 0.34	3.78 ± 1.06	1.56 ± 0.21	1.38 ± 0.82	0.72 ± 0.19	0.57 ± 0.26	0.28 ± 0.19
P_L (nmol/g)	-	0.68 ± 0.15	0.18	0.058	0.97 ± 0.53	55.7 ± 9.6	0.56 ± 0.10
P_B (nmol/mL)	-	<0.018	0.034 ± 0.007	0.0041	0.040 ± 0.015	0.11 ± 0.06	0.10 ± 0.01
P_{HPV} (nmol/mL)	-	<0.018	0.16 ± 0.09	0.035 ± 0.050	0.20 ± 0.11	2.43 ± 0.97	0.29 ± 0.08
R_{HPV-B}	0.81	2.27	0.715	0.813	0.349	0.442	0.214
P_{HPV-B}	-	<0.018	0.130	0.0303	0.158	2.32	0.195
$R_{HPV-B}/(P_{HPV-B} + R_{HPV-B})$	-	>99.9%	84.6%	96.4%	68.8%	15.9%	52.3%
$R_L/(P_L + R_L)$	-	98.1%	99.3%	99.7%	92.8%	8.5%	82.6%
R_L/R_B	**22.9**	**23.7**	**29.6**	**36.8**	**33.9**	**39.6**	**42.7**
$(R_L/R_B)_{adjusted}$	**-**	**-**	**66.4**	**410**	**58.2**	**42.8**	**64.4**
$R_{L(1+5h)}/R_{B(1+5h)}$	24.3	24.5	31.0	39.2	37.7	44.6	44.9
$(R_{L(1+5h)}/R_{B(1+5h)})_{adjusted}$	-	-	71	524	85	49	76

HPV-B = hepatic extraction; $(R_L/R_B)_{adjusted} = [(R_L/R_B)_P - (R_L/R_B)_R \times (R_{HPV-B}/(P_{HPV-B} + R_{HPV-B})]/[P_{HPV-B}/(P_{HPV-B} + R_{HPV-B})]$ = prodrug liver-targeting efficiency.

RESULTS

Oral rosuvastatin has a liver-targeting efficiency (liver/blood concentration ratio, R_L/R_B) of 22.9. Prodrug LG-23 demonstrated a similar ratio (23.7) despite ~18-fold higher liver rosuvastatin level since >99.9% prodrug was converted to rosuvastatin before reaching the liver (see Table). The other five prodrug analogs showed liver-targeting efficiency significantly higher than that of oral rosuvastatin regardless of a wide range of liver rosuvastatin concentrations (1.37-12.8-fold higher than oral rosuvastatin), different percentages of prodrug conversion to metabolite rosuvastatin in the gut (15.9-96.4%), and different percentage of prodrug activation in the liver (8.5-99.7%). Once the rosuvastatin contribution derived from the gut prodrug activation was discounted by calculating the gut activation percentage, the advantage of LTP-prodrug analogs becomes more obvious (see Figures below). The improved liver-targeting efficiency remains when both values at 1 and 5 hours are analyzed (5 hour raw data not shown).





CONCLUSIONS

LTP-rosuvastatin compounds delivered higher rosuvastatin levels in the liver and achieved higher liver-targeting efficiency relative to oral rosuvastatin. LTP technology is potentially an effective strategy to increase the therapeutic index of statin and to reduce statin intolerance.

ACKNOWLEDGEMENT and CONTACT INFORMATION

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Contact: lzhi@ligand.com (Lin Zhi)