Toward safer glucocorticoid therapy of polymyalgia rheumatica

POS1332

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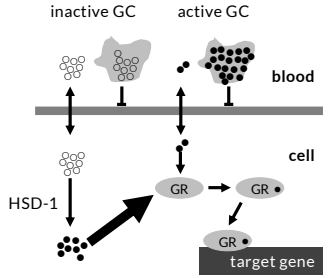
Blockade of local intracellular glucocorticoid activation by SPI-62 in target tissues mitigated glucocorticoid toxicity in mouse. These results suggest that SPI-62 has potential to similarly mitigate adverse effects of glucocorticoid medications in human.

11β-hydroxysteroid dehydrogenase (HSD) enzymes and SPI-62, a potent HSD-1 inhibitor

HSD enzymes control intracellular levels of active glucocorticoids (GC: corticosterone [CORT] in mouse, cortisol in human, and prednisolone and other GC medicines).

- HSD-1 activates GC. It is expressed in tissues (e.g., liver, adipose, bone, brain, skin, muscle, eye) in which elevated GC levels cause morbidity in mice, patients with Cushing syndrome or autonomous cortisol secretion, and patients who rely on GC medicines.
- HSD-2 inactivates GC to protect mineralocorticoid-sensitive tissues (e.g., kidney).

Much of the intracellular active GC that can act on intracellular receptors is made by HSD-1. Active GCs are highly bound by plasma proteins, so only a small fraction is free to enter cells. Inactive GC are less protein bound. They enter cells in larger quantities and are then converted to the active form, which binds receptors, translocates to the nucleus, and regulates target genes.



- SPI-62 is a potent and selective HSD-1 inhibitor.
- In Phase 1 clinical trials SPI-62 was generally well tolerated and associated with maximal liver and brain HSD-1 inhibition.

sparrow PHARMACEUTICALS

WMB is a consultant to Sparrow Pharmaceuticals.
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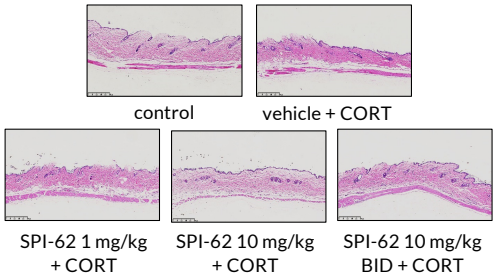
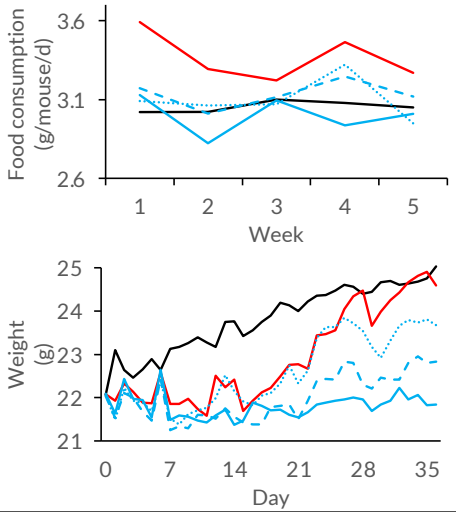
SPI-62 is investigational. This information is not for use in promotion or product commercialization.

- C57BL/6 male mice (age 7 weeks; n=14 per group) were administered CORT (100 mg/mL in drinking water) and SPI-62 (p.o.; 0, 1, or 10 mg/kg/day or 10 mg/kg 2x/day) for 35 days. Controls received no CORT or SPI-62.
- Body weight was assessed daily and food consumption twice weekly.
- Whole body muscle and fat amounts were measured at Days 0, 14, and 28 using an EchoMRI-130H body composition analyzer.
- Blood samples for fasting glucose and insulin were obtained at Days 1 (pre-dose), 15, 29, and 35.
- An open field test was conducted on Day 22 (not shown).
- A grip strength test was performed on Day 28.
- After sacrifice on Day 36, gonadal, subcutaneous, retroperitoneal, and mesenteric fat, quadriceps, and tibialis anterior were dissected and weighed, and skin was formalin fixed and paraffin embedded.



CORT effects on dermal thickness and structure were less prominent in mice who also received SPI-62



CORT resulted in increased food consumption which was normalized by SPI-62 in a dose-dependent manner. CORT-treated mice showed reduced body weight gain for 2 weeks then accelerated body weight gain. SPI-62 prevented body weight gain acceleration in a dose-dependent manner.

SPI-62 prevented CORT adverse effects of insulin resistance, increased adiposity, skeletal myoatrophy, and grip strength reduction. The table shows observed percentage difference of treatment group mean, compared to control group mean, in CORT-treated mice.

SPI-62 treatment	none	1 mg/kg 1x/day	10 mg/kg 1x/day	10 mg/kg 2x/day
HOMA-IR Day 15	+422	+428	+104	+8
HOMA-IR Day 29	+788	+472	+204	+14
HOMA-IR Day 35	+3620	+1270	+324	+92
Body fat content Day 14*	+110	+72	-13	-7
Body fat content Day 28*	+166	+102	+63	-12
Gonadal fat weight*	+151	+74	+39	-1
Subcutaneous fat weight*	+471	+121	+83	+7
Retroperitoneal fat weight*	+227	+89	+36	+25
Mesenteric fat weight*	+240	+133	+124	+71
Body muscle content Day 14*	-10	-7	0	+1
Body muscle content Day 28*	-15	-8	-6	+3
Quadriceps weight*	-54	-43	-24	-16
Tibialis anterior weight*	-35	-29	-5	+5
Grip strength	-12	+16	+15	+26

*Normalized by body weight

- **48 patients diagnosed with PMR, on stable prednisolone 10 mg for at least 1 week, and with stable disease inactivity will continue prednisolone 10 mg daily for 4 weeks and receive SPI-62 or placebo for 2 weeks each.**
- **Acute phase and other immune function biomarkers, symptom measures, and biomarkers of prednisolone adverse effects will be assessed at baseline and after each 2-week period.**
- **After review of results from a first cohort of 12 patients the prednisolone dose might be adjusted, in blinded fashion, during the SPI-62 period to maintain equipotency on acute phase biomarker suppression.**

PMR clinical trial locations