THUR-046

Repeated Treatment with AZP-3813, a Bicyclic, 16-Amino Acid Peptide Antagonist of the Human Growth Hormone Receptor, Induces Enhanced Suppression of IGF1 in Beagle Dogs

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INTRODUCTION: Medical treatment of acromegaly is based on either suppressing pituitary growth hormone (GH) secretion or inhibiting GH action by preventing interaction with its receptor in order to suppress the elevated levels of insulin-like growth factor 1 (IGF1). AZP-3813 is a 16-amino acid, bicyclic peptide antagonist of the GH receptor (GHR) derived from peptide sequences discovered using a unique, cell-free in vitro transcription-translation system screened against the human GHR, and optimized by rational design to increase binding affinity, solubility and half-life. The K_D of AZP-3813 for the human GHR is 1.9nM. In previous studies, AZP-3813 was demonstrated to suppress IGF1 secretion in juvenile rats in a dose-related manner, and to maintain IGF1 suppression when given daily for extended periods. Recently, we demonstrated that AZP-3813 is also very effective in suppressing IGF1 in normal Beagle dogs. Dogs receiving a single 0.1, 1 and 10 mg/kg subcutaneous injection of AZP-3813 responded with a dose-related 2.2 ± 7.1, 21.4 ± 2.7 and 27.8 ± 1.5% decrease in IGF1 after 24 hours, respectively, and the decrease in IGF1 attained with a single 10 mg/kg dose was maintained for over 72 hours. The relatively small further increase in IGF1 suppression with 10 versus 1 mg/kg suggests that 10 mg/kg AZP-3813 may induce near maximal GHR antagonism. In the present study, we examine the effect of repeated, 10mg/kg and higher doses of AZP-3813 treatment on IGF1 in normal Beagle dogs.

AZP-3813

16 Amino Acid, Bi-Cyclic Peptide

- MW = 2479.9
- Human GH-R affinity (K_D) = 2.9nM
- Human GH-R antagonism (IC_{50}) = 9.9nM

Half-Life in Rat

- $T^1/_2$ = 11.2 hours

Half-Life in Dog

- $T^1/_2$ = 14.2 hours

FIG 1: Dose-related suppression of IGF1 in juvenile rats with single injection of AZP-3813 (data normalized to pre-dose levels; means ± SEM)

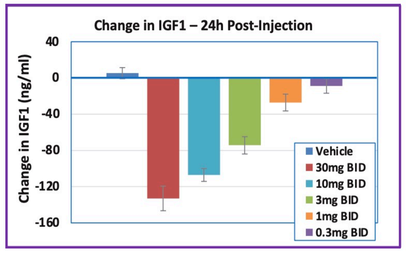


FIG 2: Suppression of IGF1 in juvenile rats maintained with repeated, daily AZP-3813 injection versus pegvisomant (means ± SEM)

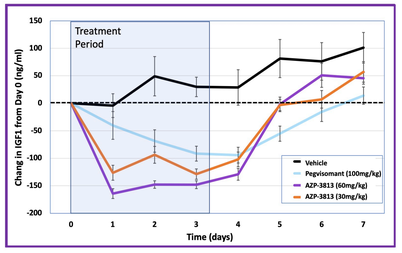


FIG 3: Dose-related suppression of IGF1 24h after single AZP-3813 injection in Beagle dogs (means ± SEM)

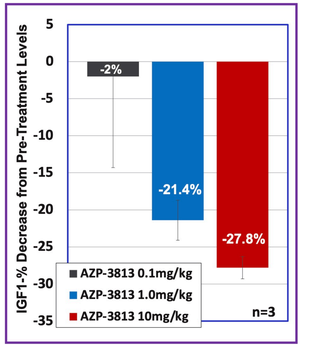


FIG 4: A) Repeated injection of 1mg/kg AZP-3813 maintains IGF1 suppression, and B) Sustained suppression of IGF1 with single injection of 10mg/kg (means ± SEM)

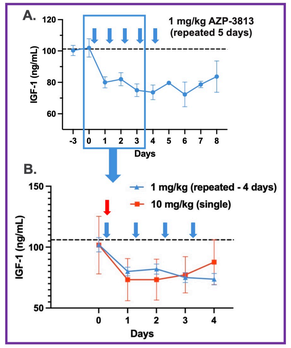


FIG 5: Study Design – Seven days repeated injection of 10, 30 or 60mg/kg AZP-3813 in male Beagle dogs (n=2/dose, one male, one female. Weight = 8.4 - 9.9kg for males and 7.7 – 8.2kg for females at dosing initiation)

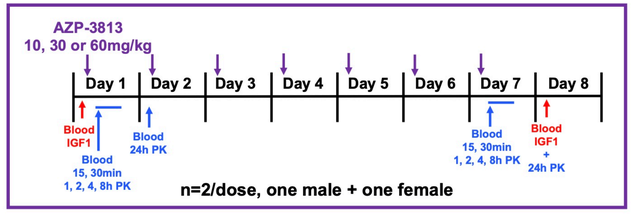


FIG 6: Daily injection of 10, 30 or 60mg/kg AZP-3813 for 7 days resulted in similar IGF1 suppression. While baseline levels were lower in females (136.7 ± 36.1 vs. 197.0 ± 11.3 ng/ml for males) the percent suppression was similar and results were combined.

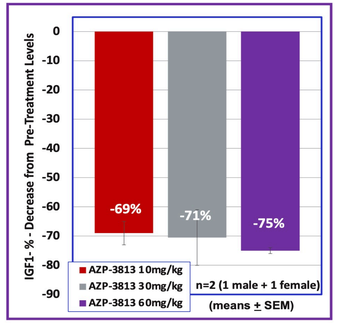


FIG 7: Daily injection of 10, 30 or 60mg/kg AZP-3813 for 7 days resulted in higher, though non-significant, levels of serum GH in Beagle dogs (data similar and combined for all three doses: means ± SEM)

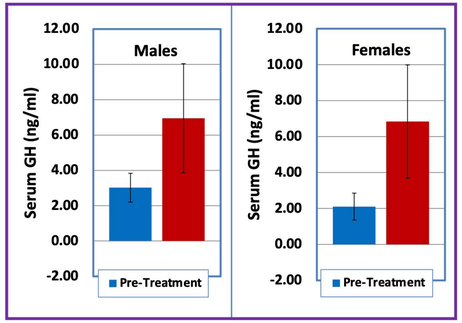
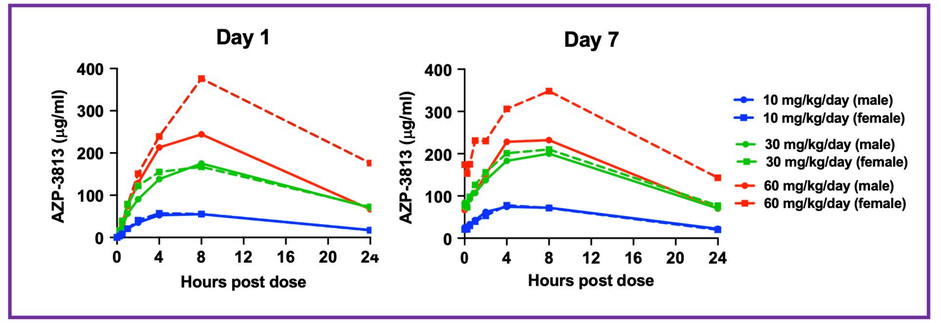


FIG 8: Similar pharmacokinetic profiles of AZP-3813 blood levels after initial injection (day 1) and after 7 days repeated injection of 10, 30 or 60mg/kg AZP-3813), suggesting that the increased suppression of IGF1 observed after 7 days may not have been due to compound accumulation. Note, however, increased blood levels at early times after injection on day 7, indicating residual compound from prior injections.



Summary of Effects of Repeated Injection of AZP-3813 in Normal Beagle Dogs:

- Significantly greater suppression of IGF1 was achieved with 7 days repeated injection of AZP-3813 at doses of 10mg/kg and above (FIG. 6) as compared with single injection (FIG. 3 and 4). The similar suppression of IGF1 with all three doses of AZP-3813 indicate that maximal effect was achieved with the lowest dose tested, 10mg/kg.
- A clear, though statistically non-significant increase in GH levels, was observed that was most likely the result of loss of negative IGF1 feedback.
- The pharmacokinetic profile of AZP-3813 was similar after the initial injection on day 1 and the final injection on day 7, suggesting that the increased suppression of IGF1 after 7 days treatment may have been due to a progressive effect of maximal GH antagonism on IGF1 production rather than compound accumulation.

CONCLUSION:

These results demonstrate that with continued treatment, the potent GHR antagonist activity exhibited by AZP-3813 translates to highly effective, in vivo suppression of IGF1 levels in normal Beagle dogs, and further support its development as a potential therapy for acromegaly.

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