MON-110

ENDO2024

Enhanced Ability of the Small Peptide GH Receptor Antagonist, AZP-3813 to Decrease IGF-1 When Combined with the Somatostatin Analog, Octreotide

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INTRODUCTION

The goal in treating acromegaly is to normalize the excess circulating IGF-1 to alleviate the associated symptoms and manage potential medical complications. Three therapeutic approaches currently exist to treat acromegaly: 1) surgery, 2) medicinal therapy (with somatostatin analogs (SSAs), growth hormone receptor antagonist (GHRA) and dopamine agonists) and 3) radiotherapy. While surgery is potentially curative, it fails in approximately 60% of patients. The majority of patients for whom surgery fails are currently medically treated with SSAs; however, normalization of IGF-1 is achieved in less than 40%.

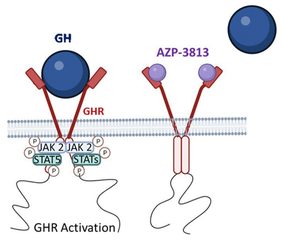
AZP-3813 is a 16-amino acid, bicyclic peptide antagonist with high affinity for the GHR and an inherently long half life in the blood stream. It was selected for clinical development as add-on therapy to SSAs in patients with acromegaly inadequately controlled by SSAs. Recently, we demonstrated that AZP-3813 is effective in suppressing IGF-1 in juvenile and adult rats, normal Beagle dogs and in healthy individuals. Here, the effect of subcutaneous administrations of AZP-3813 on circulating IGF-1 levels was examined in normal rats when administered in combination with the SSA, octreotide.

AZP-3813

16 amino acid bicyclic peptide
Molecular weight (MW) = 2479.9 Da

Human GH-R affinity (K_D) = 1.9nM
Human GH-R antagonism (IC_{50}) = 29nM

Half-life in rat ($t_{1/2}$) = 11.2 hours
Half-life in dog ($t_{1/2}$) = 14.2 hours



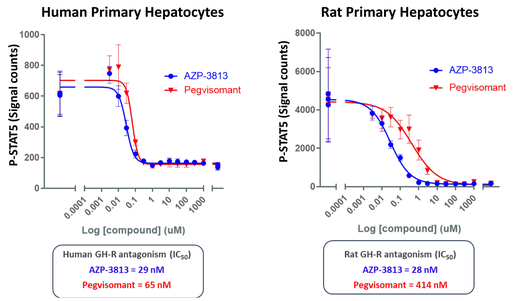


FIG 1: Human primary hepatocytes treated with 10 nM (ED80) of human recombinant GH and rat primary hepatocytes treated with 31 nM (ED80) of rat recombinant GH followed by treatment with either AZP-3813 or pegvisomant, a GHRA (means ± SD in AlphaLISA® SureFire® Ultra™ p-STAT5 (Tyr694/699); n=9 replicates)

AZP-3813 EFFECTS AFTER DAILY SUBCUTANEOUS INJECTIONS FOR 19 DAYS IN JUVENILE RATS

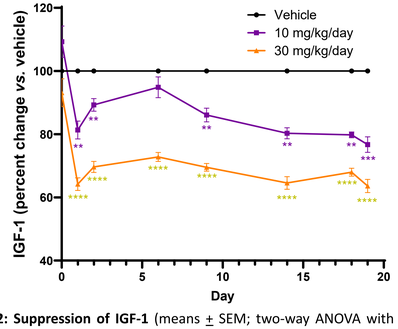


FIG 2: Suppression of IGF-1 (means ± SEM; two-way ANOVA with Dunnett's multiple comparisons test; ****p<0.0001; ***p<0.001; **p<0.01; n=7/group)

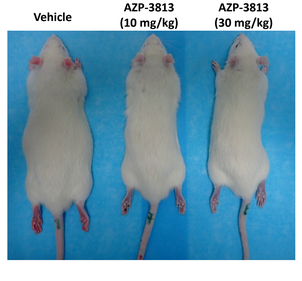


FIG 3: Reduced body growth in juvenile rats given 10 or 30 mg/kg of AZP-3813 (representative photograph)

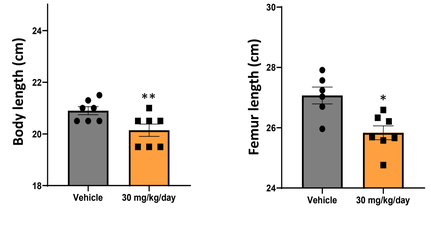


FIG 4: Reduced body and femur lengths in juvenile rats given 30 mg/kg of AZP-3813 (means ± SEM; *p<0.05; **p<0.01; n=7/group)

ADDITIVE EFFECT OF CO-ADMINISTRATION OF OCTREOTIDE AND AZP-3813 IN YOUNG ADULT RATS

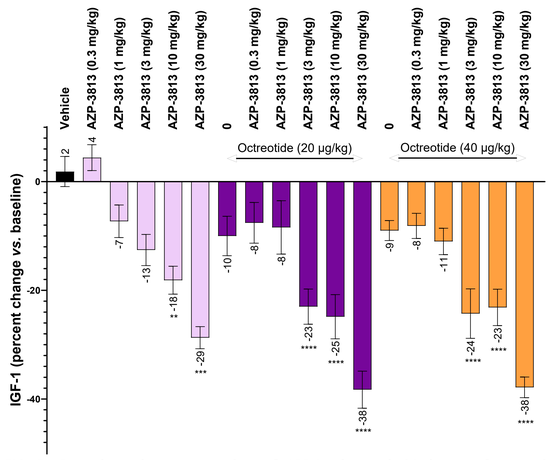


FIG 5: Dose-dependent suppression of IGF-1 observed 24 hours after a single subcutaneous injection of AZP-3813 administered either alone or in combination with infused octreotide. AZP-3813 was administered 72 hours after initiating octreotide infusion(means ± SEM; one-way ANOVA followed by Tukey's multiple comparison test; **p<0.01; ***p<0.001; ****p<0.0001 in AZP-3813 +/- octreotide vs. control vehicle groups; n=7/group)

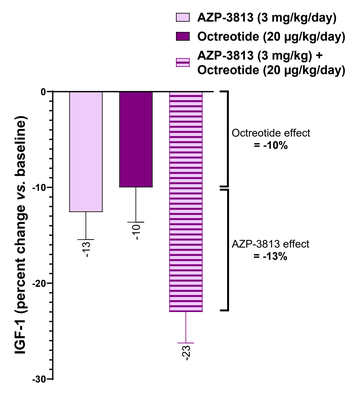


FIG 6: Additive effect of octreotide and AZP-3813 in suppressing serum IGF-1 levels exemplified by AZP-3813 at the dose of 3 mg/kg (means ± SEM; n=7/group)

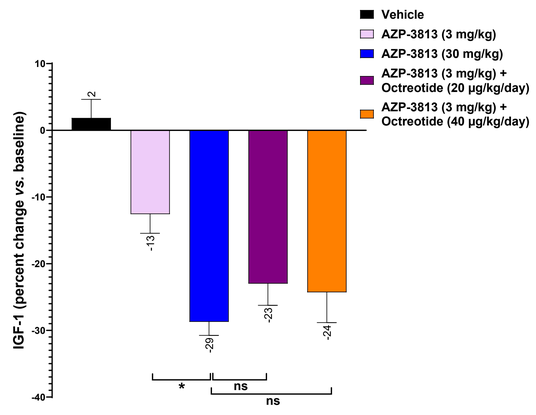


FIG 7: Octreotide administration reduces the dose of AZP-3813 required for maximum reduction of circulating IGF-1 levels (means ± SEM; one-way ANOVA followed by Tukey's multiple comparison test; ns=not significant; *p<0.05 in AZP-3813 at 3 mg/kg + octreotide vs. AZP-3813 at 30 mg/kg alone; n=7/group)

SUMMARY AND CONCLUSION

The results presented here demonstrate that AZP-3813 binds to the GHR with high affinity and, consequently, inhibits GH-stimulated activation of STAT5. The antagonistic effect of AZP-3813 on the GHR leads to a dose-dependent decrease of circulating IGF-1 levels *in vivo*. In juvenile rats, prolonged AZP-3813 treatment decreased body size and femur length, demonstrating that AZP-3813 inhibits GH and IGF-1 action on their target tissues. Co-administration of AZP-3813 with the SSA, octreotide, revealed an additive effect in suppressing circulating IGF-1 levels in rats, and reduced by ten-fold the AZP-3813 dose needed to induce a maximum decrease in IGF-1. These results illustrate the enhanced efficacy of AZP-3813 in suppressing IGF-1 when combined with the SSA, octreotide, and support the use of AZP-3813 as add-on therapy in patients inadequately controlled with SSA treatment.

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