AG10, an orally available, novel transthyretin (TTR) stabilizer: integrated preclinical evaluation predicts a highly effective treatment for TTR amyloid cardiomyopathy

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Introduction

TTR amyloid cardiomyopathy (ATTR-CM) is a degenerative disease caused by TTR tetramer dissociation, monomer misfolding, aggregation and myocardial deposition of toxic TTR amyloid aggregates. Missense mutations in TTR resulting in less stable tetramers cause an autosomal dominant form of the disease (ATTRm-CM) that is generally more aggressive than that associated with wild-type TTR (ATTRwt-CM). Individuals carrying the trans-suppressor T119M variant together with the polyneuropathy (ATTR-PN) associated V30M-TTR mutation, present a more benign evolution of ATTR-PN or no disease compared to heterozygote kindred carrying the V30M-TTR mutation alone. Genetic, structural and clinical evidence (dilusional and tafamidosis trials in ATTR-PN) suggests that TTR stabilization may be an effective disease-modifying strategy for ATTR-CM. No therapies are currently approved to treat ATTR-CM.

Purpose

To document the therapeutic potential of AG10¹-² for treating ATTR-CM based on in vitro and in vivo demonstration of TTR stabilizing activity.

Methods

Due to the lack of animal models that faithfully reproduce the pathology of human ATTR-CM, new approaches to test the efficacy of TTR kinetic stabilizers are greatly needed. We took a comprehensive structural and biochemical approach in vitro and in vivo (in dogs) to characterize the TTR-stabilizing activity of AG10. Structural studies were used to document and characterize the nature of binding between AG10 and TTR at the thyrinocin binding sites. Following oral dosing of AG10 to dogs, a combination of ex vivo fluorescence and western blot assays characterized the ability of AG10 to occupy and stabilize the TTR tetramer, preventing dissociation and amyloidogenesis.

Results

Figure 1. AG10 stabilizes TTR in human serum in vitro more effectively than other known stabilizers

Figure 2. AG10 stabilizes TTR by mimicking the disease suppressing T119M variant

Figure 3. AG10 effectively stabilizes TTR in beagle dog serum in vitro

Figure 4. Orally administered AG10 effectively stabilizes TTR in beagle dogs serum ex vivo

Conclusion

AG10 participates in potent, specific, unique and unprecedented binding interactions with TTR that mimic the protective T119M mutation, as reflected in structural, biochemical, and in vivo studies. Despite the limitations of available animal models, the healthy dog presents an informative nonclinical model for exploring the PK-PD relationships of orally available, small molecule TTR stabilizers like AG10.

References:

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