AT-001 Significantly Reduces Cardiac Damage in an Animal Model of Diabetic Cardiomyopathy

POSTER #1119

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Introduction

Hyperactive flux through the polyol pathway contributes to development of diabetic complications[1]. Aldose reductase (AR) is the rate-controlling enzyme in the polyol pathway that catalyzes NADPH-dependent reduction of glucose to sorbitol. During hyperglycemic and ischemic conditions, increased polyol pathway flux causes a rise in intracellular sorbitol and consequent changes in cytosolic NAD+/NADH, oxidative stress, cell death, and diabetic complications such as Diabetic Cardiomyopathy (DbCM).[2,3] Previous efforts to target this pathway using AR inhibitors (ARIs) have been limited by unfavorable benefit risk profiles. AT-001 is a novel oral ARI with optimized specificity and affinity for AR.

Objectives

We assessed target engagement (Study 001) and cardioprotective activity in a cardiac ischemia reperfusion (IR) injury model† (Study 002) in two rodent type 2 diabetes (DM) models.

Methodology

Study 001: Diabetes was induced in Sprague-Dawley rats by a single intraperitoneal injection 55 mg/kg streptozotocin (STZ). DM rats were orally gavaged with AT-001 5 mg/kg, 10mg/kg or vehicle (n=5 per group). Erythrocyte sorbitol was measured at 0, 7, 24 and 48 h after dosing.

Study 002: Transgenic mice expressing human levels of aldose reductase (Tg hAR) were treated with STZ (55 mg/kg for 5 days at age 6 weeks). Tg hAR mice with DM, defined as blood glucose >250 mg/dL confirmed twice for 3 weeks were treated with AT-001 40 mg/kg (n=6) or vehicle (V, n=6) for 3 days prior to IR injury induced by in vivo ligation and reperfusion of the left anterior descending (LAD) coronary artery. Control non-DM Tg hAR mice (non-DM, n=9) were also subjected to IR injury. Fractional shortening fraction (FS) was assessed by echocardiography prior to LAD ligation and after 48 h recovery. Mice were euthanized after 48 h and infarct area in hearts assessed using 2,3,5-triphenyltetrazolium chloride staining and expressed as a ratio of infarcted to total left ventricular (LV) area.

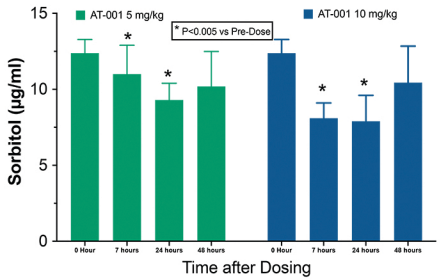
Results

STUDY 001

Prior to treatment, sorbitol was elevated in DM compared with non-DM rats: 12.38±0.9 vs 9.45±1.45 µg/ml

- Both AT-001 doses reduced sorbitol significantly and 10 mg/kg dose normalized sorbitol to the non-DM level **(Figure 1)**
  - sorbitol levels were 9.3±1.1, 7.9±1.7, and 9.45±1.3 µg/ml for AT-001 5 mg/kg, 10 mg/kg, and non-DM, respectively
- The efficacy was sustained for 24h

FIGURE 1
Mean (±SEM) Erythrocyte Sorbitol at Baseline over 48-h After Dosing



STUDY 002

Group 1: Tg hAR non-DM (n=9)
Group 2 Tg hAR DM + Vehicle (n=6)
Group 3: Tg hAR DM + AT-001 (n=6)

Blood glucose was significantly lower in non-DM vs. vehicle and AT-001 treated DM rats (112±21 vs 353±76 and 426±102 mg/dL, respectively). Heart rate and FS were similar in all groups prior to LAD ligation.

After 48h reperfusion functional recovery, fractional shortening (FS) was improved only in AT-001 treated hearts **(Figure 2)**.

AT-001 significantly reduced infarct size **(Figure 3)** and improved FS, expressed as a % of baseline compared with both the vehicle and non-DM groups (P<0.001) **(Figure 2)**.

Results (cont'd)

FIGURE 2
Mean (±SEM) Fractional Shortening

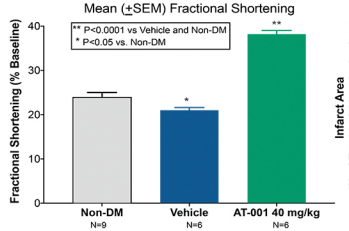
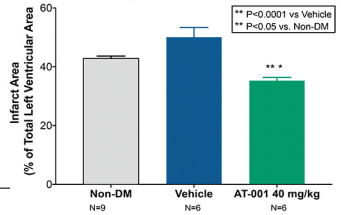


FIGURE 3
Mean (±SEM) Infarct Area



†The ischemia reperfusion (IR) injury model of cardiac damage in AR transgenic mice has been validated as a relevant animal model for DbCM.[4] Mice naturally express very low levels of AR vs. humans, so over-expression to achieve human levels has been suggested as a more accurate model of human cardiac damage in diabetes. Cardiac damage caused by IR is greater in diabetic animals vs. non-diabetic animals, implicating AR as a key mechanism of cardiac damage during diabetes. Inhibition of AR with AT-001 reduced cardiac damage significantly in the IR model, as measured by infarct area and fractional shortening.

Conclusion

AT-001 normalized sorbitol levels relative to non-DM control rats, demonstrating effective inhibition of AR.

AT-001 significantly reduced cardiac damage in a relevant mouse model of DbCM. At 48-h post reperfusion, both infarct area and functional recovery, defined by FS relative to baseline were improved only in AT-001 treated rats.

These findings:

- Confirm biological activity of AT-001
- Demonstrate the role of AR inhibition in significantly reducing or preventing cardiac damage
- Support clinical investigation of AT-001 in DbCM

References

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DISCLOSURES: SS and RP are employees of and stockholders in Applied Therapeutics Inc.

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