Abstract: 56

The SGLT2 inhibitor empagliflozin reduces mortality in experimental pulmonary hypertension

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Introduction: Empagliflozin, a sodium-glucose co-transporter 2 (SGLT2) inhibitor, enhances urinary glucose excretion and profoundly reduces hospitalisation for heart failure and cardiovascular mortality in individuals with type 2 diabetes. While empagliflozin has been reported to reduce blood pressure, its effect on pulmonary arterial hypertension (PAH) is unknown. PAH is a serious and progressive disease that is characterised by pulmonary artery vasoconstriction, vascular remodelling, right ventricular hypertrophy, and ultimately heart failure.

Purpose: To investigate the impact of empagliflozin on PAH-associated mortality and the progression as well as reversal of PAH in monocrotaline (MCT)-treated Sprague-Dawley rats.

Methods: A total of 66 male rats (220-250 g) were randomly assigned to one of three studies. PAH was induced with a single intraperitoneal injection of MCT on day 0 and empagliflozin (10 mg/kg) was administered daily by oral gavage. Survival study: PAH was induced with 60 mg/kg MCT. Starting on day 1, rats were treated with empagliflozin (n=8) or vehicle (n=8) for 28 days and monitored for up to 45 days post-MCT injection. Prevention study: Rats were administered 60 mg/kg MCT and treated with empagliflozin (n=12) or vehicle (n=12) for 20 days from day 1 onwards. Reversal study: 21 days after being injected with 40 mg/kg MCT, rats were given empagliflozin (n=8) or vehicle (n=8) for 14 days. At the end of the treatment window, rats in the latter two studies underwent haemodynamic assessments before their tissues were harvested for histological review.

Results: Mortality rates between the two groups were significantly different (median survival 24 vs 33 days for vehicle vs empagliflozin; p<0.05). Compared to the MCT-vehicle-treated rats, the MCT-empagliflozin group had significantly lower mean pulmonary artery pressure (77.4 ± 8.6 vs 51.0 ± 4.9 mmHg [Prevention study]; 56.0 ± 4.3 vs 43.0 ± 3.4 mmHg [Reversal study]); higher pulmonary acceleration time (21.0 ± 0.8 vs 27.4 ± 1.4 ms [Prevention study] and 27.1 ± 1.0 vs 33.4 ± 1.3 ms [Reversal study]); and less right ventricular hypertrophy (0.52 ± 0.01 vs 0.41 ± 0.04 [Prevention study]). Histological assessments revealed significantly less medial wall thickening (50.8 ± 2.2 vs 44.7 ± 1.1 mm) and muscularisation (53.2 ± 1.3 vs 43.6 ± 2.1 mm) in pulmonary arterioles from the empagliflozin- vs vehicle-treated rats (p<0.001 for both).

Conclusion: This is the first study demonstrating that SGLT2 inhibition with empagliflozin lowers mortality in experimental pulmonary hypertension in part via reduced pulmonary vascular remodelling.