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Cardio-renal protection of riociguat (BAY 63-2521) in low- and high-renin models of hypertension

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Background

Riociguat (BAY 63-2521) is a direct NO-independent stimulator of soluble guanylate cyclase (sGC) and is being investigated as a new therapeutic approach for the treatment of different forms of pulmonary hypertension in clinical phase III trials. The NO-sGC-cGMP signal transduction pathway is impaired in different cardiovascular diseases, including pulmonary hypertension, heart failure and arterial hypertension. We thus investigated the cardio-renal protective effects of riociguat in low-renin and high-renin rat models of hypertension.

Materials and methods

The cardiovascular consequences of sGC stimulation were evaluated by the long-term effects of riociguat in hypertensive renin-transgenic (TG(mRRen2)27) rats treated with the NOS inhibitor N-nitro-L-arginine methylester (L-NAME). This high-renin study lasted 18 days and contained 3 groups: control (n = 24), 3 mg/kg (n = 12) and 10 mg/kg (n = 12) riociguat orally once daily. Rats with 5/6 nephrectomy (5/6 NX) were used as low-renin model of hypertension. This low-renin study lasted 18 weeks and contained 3 groups: 5/6 NX (n = 15), 5/6 NX + riociguat (300 ppm in the solid feed; n = 12) and sham-operation (n = 10). Blood pressure was assessed via tail-cuff repeatedly, at the end of the study all animals were sacrificed, blood and organ samples were harvested for further studies.

Results

In the high-renin study part, the beneficial effects of riociguat are emphasized by a significantly increased survival in both dosages (riociguat low dose: 92%, riociguat high dose: 100% vs 46% in L-NAME treated rennin transgenic rats). In the low-renin study, overall survival was higher: 5/6 NX 60%, 5/6 NX + riociguat 73%, sham 100%. In both models the blood pressure was significantly reduced by riociguat. Moreover, in the high-renin study part riociguat reduced cardiac target organ damage as indicated by lower plasma ANP, lower relative left ventricular weight and lower cardiac interstitial fibrosis and reduced renal target organ damage as indicated by lower plasma creatinine and urea, less glomerulosclerosis and less renal interstitial fibrosis. In the low-renin study part riociguat reduced cardiac target organ damage as indicated by lower plasma ANP, lower relative left ventricular weight, lower myocyte diameter and lower arterial media/lumen ratio and reduced renal target organ damage as indicated by

improved creatinine clearance and less renal interstitial fibrosis.

Conclusion

We demonstrate for the first time that the novel sGC stimulator riociguat shows in two independent models of hypertension a potent protection against cardiac and renal target organ damage.