SGLT2 i Dapagliflozin reduces NF-kB expression in heart and kidneys of preclinical models exposed to doxorubicin through MYd-88 and NLRP3 pathways: an hystological study

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Background: Doxorubicin-mediated adverse cardiovascular events are among the leading causes of morbidity and mortality in breast cancer patients. Sodium-glucose cotransporter 2 (SGLT2) inhibitors have recently been shown to be of therapeutic value in patients with type 2 diabetes, chronic kidney disease, and heart failure with reduced ejection fraction (HFrEF), conditions that commonly coexist and are interrelated pathophysiologically.

Purpose: We hypothesized that Dapagliflozin (an SGLT2i), administered during doxorubicin, could improve cardiac function in preclinical models

Methods: Female C57Bl/6 mice were untreated (Sham, n=6) or treated for 10 days with doxorubicin i.p at 2.17 mg/kg (DOXO, n=6), DAPA at 12 mg/kg (DAPA, n=6) or doxorubicin combined to DAPA (DOXO-DAPA, n=6). Ejection fraction, radial and longitudinal strain were analyzed through transthoracic echocardiography (Vevo 2100). Cardiac tissue expression of NLRP3 in inflamasome, Myd88, DAMPs (galectine 3 and calgranulinS100), pAMPK, NF-kB, and 13 chemokines (IL-1α, IL-1β, IL-2, IL-4, IL-6, IL-10, IL-12, IL17-α, IL-18, IFN-γ, TNF-α, G-CSF, and GM-CSF) were quantified through ELISA and western blot methods.

Results: DAPA improved significantly the EF and prevented the reduction of radial and longitudinal strain after 10 days of treatment with doxorubicin. A reduced expression of NLRP3, Myd88, DAMPs and NF-kB in cardiac tissues was seen in DOXO-DAPA group compared to DOXO mice (p<0.001). Cardiac expression of IL-1β, IL-6, NF-kB, G-CSF and GM-CSF were significantly reduced after treatment with DAPA indicating anti-inflammatory properties. Expression of pAMPK was strongly enhanced in DAPA-DOXO compared to DOXO group. Levels of Calgranulin S100 and galectine-3 were strongly enhanced in DOXO-DAPA group; on the other hand their expression were reduced by 47.7 and 52.3% in DAPA-DOXO group vs DOXO (p<0.005). Hystology evaluation indicate reduction NF-kB expression in myocardial and renal tissue in DOXO-DAPA vs DOXO. Radial strain (RS) is 38.8% in DAPA-DOXO vs 14.1% in DOXO groups (P < 0.05); longitudinal strain (LS) is –23.4 % in DAPA-DOXO vs –10.5% in DOXO groups (P < 0.001)

Conclusion: In this preclinical study, DAPA is able to improve cardiac function and reduce biomarkers involved in heart failure and fibrosis. The overall picture of the study pushes the use of DAPA in prevention of cardiomyopathies induced by anthracyclines in cancer patients.