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Can ARNI Prevent Doxorubicin-Induced Cardiotoxicity?

LETTER TO THE EDITOR

To the Editor,

In previous issues of the journal, we have just read with great interest the article by Dindaş et al[1] entitled "Angiotensin receptor-neprilysin inhibition by sacubitril/valsartan attenuates doxorubicin-induced cardiotoxicity in a pretreatment mice model by interfering with oxidative stress, inflammation, and Caspase 3 apoptotic pathway" published in *Anatol J Cardiol* 2021; 25: 821-8.[1]

The study included a doxorubicin-induced cardiomyopathy model, and the authors demonstrated that Sacubitril/Valsartan (SAC/VAL) combination therapy can be protective against doxorubicin (Dox) induced cardiomyopathy via its anti-arrhythmic, anti-inflammatory, antioxidant, and antiapoptotic effects. However, we have major concerns regarding the methodology and results of the study.

First, it can be seen areas of irregularity, proteinaceous material accumulation, and hyperemia between the muscle fibers in the Dox treated group's histologic specimens. It was observed that degenerative changes decreased and streaking in cardiomyocytes was normal in the Sac/Val+ Dox group. These changes are very demonstrative but there are no quantitative data. We think it should have included quantitative measurements and comparisons just like infiltrative cell accumulation or necrosis markers.[2] Moreover; It should not be forgotten that histological examinations can differ according to the sites taken and the subjects. Therefore, a quantitative analysis should have been made to detect histological effects.

Secondly, imaging tools were not used in this study. It's a big deficit to detect Sac/Val's effects on left ventricular functions. Therefore, although it's claimed that this study showed a protective/preventive effect of Sac/Val in the Dox-induced cardiomyopathy pretreatment mice model, we don't think that this inference will be correct with the available data.

Finally, in the discussion section, it has been proposed that the protective effects of the SAC/VAL combination in mice hearts originate its antioxidant effects against reactive oxygen species (ROS). However, the damage of ROS is no longer a cause but a consequence of DOX cardiotoxicity. Although previous studies highlight oxidant factors in DOX cardiotoxicity,[3] recent strong evidence suggests that topoisomerase 2 β (TOPO2β) inhibition, peroxisome proliferator-activated receptor-gamma coactivator1-alpha (PGCF-1α) downregulation, and sarcoplasmic reticulum damage are the main reasons for DOX cardiotoxicity.[4] Although the increase in ROS amounts is not the main cause of toxicity, it is attributed to the degeneration resulting from the inhibition of TOPO2β and downregulation of PGC-1α.[5] Thus, we wonder whether SAC/VAL has any effects on TOPO2β inhibition and the authors should explain their results taking this into account.

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