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REVIEW:

Angiotensin-Converting Enzyme Inhibition Early After Heart Transplantation.

Fearon WF, Okada K, Kobashigawa J, Kobayashi Y, Luikart H, Sana S, Daun T, Chmura SA, Sinha S, Cohen G, Honda Y, Pham M, Lewis DB, Bernstein D, Yeung AC, Valantine HA, Khush K. J Am Coll Cardiol 2017;69:2832–41

In this issue of the "Journal Watch" I would like to draw the attention of the HF-HTx council on a recent study published by the Stanford group about ACE inhibitors in heart transplant recipients.
Inhibition of the ACE system is a cornerstone of cardiovascular protection in patients with risk factors or with previous cardiovascular events. Nevertheless, in a context of very high cardiovascular risk profile such as heart transplantation, the efficacy and safety of these therapies has never been prospectively evaluated. In addition, concerns about their safety on renal function during therapy with calcineurin inhibitors, and uncertainty about their potential utility in preventing meaningful outcomes, further limits the utilization of ACE inhibitors in heart transplant recipients.

Older studies[1-3] showed potential utility of ACE inhibitors in reducing CAV development, but the findings were limited mainly by the retrospective and non-randomized design, and by currently outdated immunosuppressive therapy.
In this paper, Fearon and colleagues studied in the first year after transplantation the effect of ramipril on IVUS-defined CAV, and on other functional and surrogate endpoints. Study design was randomized, multicentric, and placebo-controlled. Ninety-six patients were randomized to receive either ramipril at a progressively tapered dose or placebo. Immunosuppression consisted in tacrolimus for most of cases, in conjunction with mycophenolate and steroids; pravastatin was prescribed to the vast majority of patients (> 90% in both study groups), and CMV infection was prevented by a valganciclovir-based prophylaxis strategy. Calcium-channel blockers were also recommended as anti-hypertensive medications. The primary outcome measure was the progression in plaque volume in the first year. Key secondary endpoints included the safety and efficacy of ramipril administration early after HT, effect of ramipril on coronary endothelial function, coronary physiology, and circulating endothelial progenitor cell number.
Abnormalities of coronary physiology, even when measured non invasively, have been found to predict angiographic CAV development and adverse prognosis after transplantation[4]. Herein, coronary physiology has been assessed invasively by measuring microvascular function, as assessed by coronary flow reserve (CFR), index of microvascular resistance (IMR), and fractional flow reserve (FFR). It is useful to summarize the meaning of these parameters, as probably some of us are not confident with them: coronary flow reserve is the resting mean transit time divided by the hyperemic mean transit time and interrogates the ability of the entire coronary circulation, both the microcirculation

and the epicardial vessels, to vasodilate; IMR is the hyperemic mean transit time multiplied by the hyperemic distal coronary pressure, thus is an index specific for coronary microvasculature, and FFR is the mean distal pressure divided by the mean proximal pressure during maximal hyperemia (an index that independently assesses the functional significance of epicardial CAV).
While ramipril didn't show any effect compared to placebo on plaque progression, it was associated with
a decrease in IMR and FFR with an increase in CFR overall reflecting an improvement of microvascular function. Moreover, patients in ramipril group didn't have the reduction in change in the log10 quantity of circulating endothelial progenitor cells (EPCs) observed in the placebo group. Taken together, these results show that ACE-inhibitors can favourably influence microvascular function early after transplantation, that has been suggested to be a prognostic marker in this patient population, even if it doesn't seem to influence epicardial disease.
Additional clinical findings include anti-hypertensive efficacy, and overall safety, with only one patient withdrawing the drug because of hypotension, and no cases of acute kidney dysfunction or hyperkaliemia.
There are several limitations in this study, including the limited sample size and the short follow up that does not allow analyses on clinically meaningful events. However, I believe that this study provides an important piece of knowledge for the management of heart transplant patients by providing reassuring data on ACE inhibitors safety and anti-hypertensive efficacy, and by suggesting potential vascular protection of the graft.

ADDITIONAL ARTICLES OF INTEREST:

1. Mehra MR, Ventura HO, Smart FW, Collins TJ, Ramee SR, Stapleton DD. An intravascular ultrasound study of the influence of angiotensinconverting enzyme inhibitors and calcium entry blockers on the development of cardiac allograft vasculopathy. Am J Cardiol 1995;75:853–4.

2. Erinc K, Yamani MH, Starling RC, Crowe T, Hobbs R, Bott-Silverman C, Rincon G, Young JB, Feng J, Cook DJ, Smedira N, Tuzcu EM. The effect of combined angiotensin-converting enzyme inhibition and calcium antagonism on allograft coronary vasculopathy validated by intravascular ultrasound. J Heart Lung Transplant 2005;24:1033–8.

3. Bae JH, Rihal CS, Edwards BS, Kushwaha SS, Mathew V, Prasad A, Holmes DR Jr, Lerman A. Association of angiotensin-converting enzyme inhibitors and serum lipids with plaque regression in cardiac allograft vasculopathy. Transplantation 2006;82: 1108–11.

4. Tona F, Osto E, Famoso G, Previato M, Fedrigo M, Vecchiati A, Perazzolo Marra M, Tellatin S, Bellu R, Tarantini G, Feltrin G, Angelini A, Thiene G, Gerosa G, Iliceto S. Coronary microvascular dysfunction correlates with the new onset of cardiac allograft vasculopathy in heart transplant patients with normal coroanry angiography. Am J Transplant. 2015 May;15(5):1400-6