TARGETING THE RENIN-ANGIOTENSIN SYSTEM: POTENTIAL BENEFICIAL EFFECTS OF THE ANGIOTENSIN II RECEPTOR BLOCKERS IN PATIENTS WITH NASH

Silvia Sookoian[1] MD, PhD, and Carlos J Pirola[2] PhD

[1]Department of Clinical and Molecular Hepatology, Institute of Medical Research A Lanari-IDIM, University of Buenos Aires-National Council of Scientific and Technological Research (CONICET), Ciudad Autónoma de Buenos Aires, Argentina.

[2]Department of Molecular Genetics and Biology of Complex Diseases, Institute of Medical Research A Lanari-IDIM, University of Buenos Aires-National-Council of Scientific and Technological Research (CONICET), Ciudad Autónoma de Buenos Aires, Argentina.

Author for correspondence:

Silvia Sookoian, MD, PhD.

Instituto de Investigaciones Médicas IDIM-CONICET.

Av. Combatiente de Malvinas 3150.

(1427) Buenos Aires. Argentina.

TE: 54-11-4514 8701 ext 167. FAX: 54-11-4523 8947

ssookoian@lanari.fmed.uba.ar

FUNDING SUPPORT

This study was partially supported by grants PICT 2008-1521 (Agencia Nacional de Promoción Científica y Tecnológica), and UBACYT CM04 (Universidad de Buenos Aires). SS and CJP belong to CONICET.

To the Editor:

We read with great interest the article by Torres DM et al. about the efficacy of combination therapy with rosiglitazone and metformin or losartan on improving liver histology in patients with NAFLD; the authors conclude that adjuvant therapies are ineffective (1). It is certainly a very interesting study to find out some prospect ideas about the therapeutic potential of "combination effects" or "combination therapy," as we are still uncertain as to whether or not disregarding combination therapy is a good option for NASH patients. As discussed by the authors, an interesting drug to consider is telmisartan, which also acts as a partial agonist of *PPARγ*. In fact, in addition to the observed effects on fatty liver reversion, telmisartan is able to improve insulin resistance, but it is less effective than losartan in preventing plasminogen activator inhibitor-1 gene expression (2). Therefore, combining both actions in one molecule may improve some aspects of NASH but not all of them.

At any rate, there are other reasons to think about the importance of the blockade of the renin-angiotensin system (RAS) in the liver of NASH patients. Perhaps in the study of Torres DM et al., improvement in body weight was not as expected, as treatment with thiazolidinediones may prevent an interesting and poorly explored effect of angiotensin receptor blockers (ARBs) on the regulation of body weight (2). In addition, we recently observed a local upregulation of the angiotensin I-converting enzyme in the liver of patients with NASH, suggesting a putative role of the RAS in the progression of liver histology (3). Finally, the authors speculated that both environmental and genetic influences are likely involved in the lack of universal improvement observed in the patients enrolled in this trial. Can we expect that all patients are equally responders to the therapy? Certainly, we cannot.

We previously showed that a gene variant (A1166C) in the angiotensin II type 1 receptor predicts the therapeutic response to losartan; we found a higher response to losartan among AA homozygous (4). We wonder if before discharging ARBs, we might improve our ability to select patients who are able to respond better, tailoring the therapy, depending on their genetic background.

REFERENCES

1. Torres D, Jones F, Shaw J, Williams C, Ward J, Harrison S. Rosiglitazone versus rosiglitazone and metformin versus rosiglitazone and losartan in the treatment of nonalcoholic steatohepatitis (NASH): A 12 month-randomized, prospective, open-label trial. Hepatology 2011.

2. Rosselli MS, Burgueno AL, Carabelli J, Schuman M, Pirola CJ, Sookoian S. Losartan reduces liver expression of plasminogen activator inhibitor-1 (PAI-1) in a high fat-induced rat nonalcoholic fatty liver disease model. Atherosclerosis 2009;206(1):119-126.

3. Sookoian S, Gianotti TF, Rosselli MS, Burgueno AL, Castano GO, Pirola CJ. Liver transcriptional profile of atherosclerosis-related genes in human nonalcoholic fatty liver disease. Atherosclerosis 2011.

4. Sookoian S, Castano G, Garcia SI, Viudez P, Gonzalez C, Pirola CJ. A1166C angiotensin II type 1 receptor gene polymorphism may predict hemodynamic response to losartan in patients with cirrhosis and portal hypertension. Am J Gastroenterol 2005;100(3):636-642.