International Journal
of
Pharmacy Review & Research
www.ijprr.com

e-ISSN: 2248 – 9207
Print ISSN: 2248 – 9193

ASSOCIATION OF ANGIOTENSIN I CONVERTING ENZYME INHIBITORS WITH THE ANGIOTENSIN II RECEPTORS ANTAGONISTS

Gérsika bitencourt santos[1*], Camilo molino guidoni[2], Francisco R. Lello santos[3], Maria luiza pereira nunes[4], Paulo roque obrelli-neto[5], Rodrigo dos santos diniz[6], André De oliveira baldoni[7]

[1]Pharmacist, PhD student in Pharmaceutical Sciences, Therapeutic Care and Pharmacology Professor of Medicine course at Universidade José do Rosário Vellano (UNIFENAS).
[2]Pharm.D in Pharmaceutical Sciences, Clinical Pharmacy Professor at Universidade Estadual de Londrina (UEL).
[3]Medical Doctor of Nephrology, Faculty of Medicine of University of São Paulo FMUSP-SP, nephrology professor at Universidade José do Rosário Vellano (UNIFENAS).
[4]Medical Student at Universidade José do Rosário Vellano (UNIFENAS).
[5]Pharmacist with Post-doctorate in Pharmaceutical Sciences, Professor of Clinical Pharmacy at Faculdades Integradas de Ourinhos (FIO).
[6]PhD Pharmacist in Health Sciences, Professor of Pharmaceutical Assistance at Campina Grande (UFCG).
[7]PhD Pharmacist in Pharmaceutical Sciences, Professor of Clinical Pharmacy at Universidade Federal de São João Del Rei (UFSJ).

ABSTRACT

Reviewing the pharmacologic basis from the association of an angiotensin-converting enzym inhibitor drug with an antagonist of angiotensin II receptors and discuss the advantages and disadvantages of this possible association in certain clinical conditions. Literature revision using PubMed, ScienceDirect, SciELO and BIREME databases. Articles with available and relevant full texts on the combination of two renin-angiotensin-aldosterone system inhibitor drugs have been selected. The studies performed so far differ from one another. Some of them have shown that at short-term the combination therapy is superior to the inhibition of angiotensin converting enzyme on monotherapy in reducing proteinuria in patients with diabetic nephropathy. Other conclude that although a greater reduction in blood pressure in the combined therapy group when compared to the monotherapy group, no significant benefit was observed among patients who received the two-drug therapy. For more solid conclusions, new more careful approaches should be evaluated by randomized studies in patients approached individually in order to the combination therapy is not abandoned without evidence that the RAAS double blockade is not really the best option for selected patients.

Key words: Angiotensin receptor blockers, Angiotensin-converting enzyme inhibitors, rational use, Pharmacotherapy, renin-angiotensin-aldosterone system double blockade.

INTRODUCTION

The renin-angiotensin-aldosterone system (RAAS) has always been target of large studies because of its importance in the genesis of various diseases such as hypertension, acute myocardial infarction, congestive heart failure, cardiac arrhythmias, diabetes mellitus, chronic renal failure and cerebralvascular accident [1]. Although well known, new components of the RAAS are being discovered and therefore new questions arise especially regarding the inhibition of this system for the treatment of such pathological conditions.

In the last decades several studies have shown that the RAAS presents a higher complexity than It was previously thought. It was believed that the renin-angiotensin-aldosterone system was a component of the

[*]**Corresponding Author Gérsika bitencourt santos** E mail: gersika.santos@unifenas.br

endocrine system, since angiotensin II would be generated exclusively in blood distributing to the tissues through the bloodstream [2]. Nowadays, however, it is believed in the existence of several local renin-angiotensin systems containing all the required components for the production of Angiotensin II distributed in different organs which contribute to tissue homeostatic mechanisms of more slowly development and more permanent nature, such as cell growth, vascular proliferation, endothelium function modulation and matrix formation of tissues [3].

Furthermore, studies have demonstrated the involvement of other enzymes in addition to the angiotensin-converting enzyme (ACE) in the generation of angiotensin II [4]. ACE, located in the vascular endothelium plays an important role in Angiotensin II generation and it acts systemically, once the renin produced in the juxtaglomerular apparatus is released in the bloodstream to act on angiotensinogen conversion to angiotensin I^1. However, angiotensin II may also be converted from angiotensin I by a number of other peptidases, which has been mentioned in the literature as alternative pathways of angiotensin II generation.

Several existing proteases in many parts of the body are capable of producing angiotensin II in vitro through cleavage of angiotensin I, such as, trypsin, kallikrein and cathepsin G^2. More recently, a serine protease named chymase, has received attention because of its importance as an alternative pathway in the formation of Angiotensin II in several places, mainly in the heart and blood vessels [5].

Consistent mapping of angiotensin II formation alternative pathways has gained prominence especially after the development of angiotensin II receptor antagonists (AT1) such as losartan, which allowed expanding the range of therapeutical interventions in the RAAS blocked before only by ACE inhibiting drugs such as captopril.

It is noticed that the renin-angiotensin-aldo sterone system, although well known and studied, has much to be exploited for the development of new effective and beneficial treatments for patients. The objective of this article is, therefore, to review the main studies in the area and discuss about that possible association in certain clinical conditions.

METHODS

The searches were conducted in four bibliographic databases - PubMed, ScienceDirect, Sielo and BIREME. At the end of the search of each base, duplicate references were deleted. Articles published between 2007 and 2015 written in English or Portuguese were selected. The survey was conducted between December 2015 to May 2016.

As for the search terms it was opted for free terms without the use of controlled vocabulary (descriptors). With this strategy there was a recovery of a greater number of references, ensuring the detection of most papers published within the pre-established criteria. The terms angiotensin receptor blockers, angiotensin converting enzyme inhibitors, rational use, Pharmacotherapy, dual blockade of renin-angiotensin-aldosterone system were used in combination to perform the searches. Represented inclusion criteria: original and relevant study with content available in full in English or Portuguese language.

RESULTS AND DISCUSSION

The beneficial effects of the angiotensin-converting enzyme inhibitors are well known mainly in the hypertension and heart failure treatment [6-8]. However, it has been shown that patients chronically treated with effective doses of ACE-inhibitors did not have the suppression of the angiotensin II formation suggesting the involvement of alternative pathways in the generation of angiotensin [9, 10]. The "aldosterone escape" is also observed in both treatments with ACE inhibitors and with ARB (angiotensin II receptor blocker) also called angiotensin II receptor antagonists, possibly due to increased levels of potassium in blood and the formation of Angiotensin II by alternativas pathways [11]. Actually, as already mentioned, ACE inhibitors cannot block the alternative pathways and for this reason, the renin, angiotensin II and aldosterone levels often return to pre-treatment levels, since the inhibition of ACE leads to an increase of serine protease chymase activity. This "escape" may be of importance for explaining a small renoprotective effect observed in some patients treated with ACE inhibitors in the long term [12].

The action of the AT1 receptor blockers of Angiotensin II, in turn, appears to be longer lasting. Nevertheless, their use also increases the production of angiotensin II by 'upregulation' due to the blockade of AT1 receptors [13]. Angiotensin II produced can then bind to the AT1 receptors not blocked and also the AT2 receptors, that are not antagonized by ARB, which function is not well established yet. However, studies suggest that AT2 receptors are predominantly expressed in fetal tissues and also in cases of injury; furthermore, they seem to be activated by angiotensin II and angiotensin 1-7 leading to vasodilatation and anti-proliferative effects [14].

Note, therefore, that the single blockage with ACE inhibitors or ARB can achieve only partial suppression and not lasting of RAAS. Thus, it was hypothesized that the double blockade with these two classes of drugs would be more beneficial than any other agent alone.

The vast majority of studies that tested the combination of an ACE inhibitor with an ARB evaluates such therapy in chronic kidney disease (CKD) [15]. Deregulation of RAAS has an important role in the pathogenesis of CKD. There is a glomerular capillary pressure increase due to continuous stimulation of RAAS, which increases oxidative stress and stimulates proinflammatory pathways. These mechanisms cause glomerular hypertrophy, which is present at an early stage of CKD and represents the beginning of the fibrotic cascade [16].

A meta-analysis published in 2007 assessed the studies performed to date on the combination therapy of ACE inhibitor and ARB in diabetic nephropathy. It was

suggested that in the short term the combination therapy is superior to ACE inhibition on monotherapy in reducing proteinuria in patients with diabetic nephropathy. Given the lack of studies with duration of more than 12 weeks this meta-analysis was not able to provide na overview on the effect of RAAS double blockade in the long term [17].

The following year, the large ONTARGET study was published in which compared the ramipril monotherapy with the combination of ramipril and telmisartan in 25,620 patients with vascular disease or diabetes with end-organ damage. Surprisingly, despite a greater reduction in blood pressure in the combined therapy group in comparison with ramipril group alone, no significant benefit was observed among patients receiving the two-drug therapy. Furthermore, the combined therapy increased significantly the risk of hypotension, syncope, hyperkalemia and renal dysfunction with requiring dialysis [18].

However, some authors believe that the population selected in the ONTARGET study was not ideal to evaluate whether the combination therapy slows the progression of renal disease, since the vast majority of patients showed albumin excretion within normal range [19, 20]. It has been shown that ACE inhibitors and ARB reduce the loss rate of renal function in diabetic and nondiabetic CKD, but this effect is higher in patients with evident proteinuria [21, 22].

Based on this, in 2009, the VA Nephron randomized study was designed to compare the lisinopril and losartan combination therapy with losartan monotherapy in diabetic patients with evident proteinuria [23]. The study was early stopped due to adverse effects such as hypotension, hyperkalemia and acute renal injury. However, at the time of the study closure, the dual combination had already reduced end stage kidney disease events by 34% compared to losartan alone. According to authors the opportunity to clinically demonstrate nephroprotection relevant to the combination of ACEI and ARB has been lost due to the interruption of the study and they still believe that the adverse effects could be prevented by avoiding high doses of ACE inhibitors in patients with low glomerular filtration rate [24].

A different therapeutic strategy based on the combination of lower doses than recommended of an ACE inhibitor and an ARB has been suggested to effectively block the renin-angiotensin system without excessive effects of blood pressure lowering and side effects. A randomized clinical trial compared the combined therapy of enalapril 10 mg / day and losartan monotherapy 50mg / day with enalapril 20 mg / day or losartan 100mg / day in 30 patients with type 2 diabetes with overt nephropathy. Noticed greater reduction in proteinuria in combination therapy with lower doses than in the monotherapy of full doses [24]. However, this study lasted only eight weeks, and thus did not assess the therapy chronicity.

It is true that the previous long-term experience with double blockade is quite small with the exception of the cooperate assay, which demonstrated that the combination of losartan and trandolapril was significantly better than each individual drug in nondiabetic patients with moderately reduced renal function and moderated daily urinary protein excretion[25]. Unfortunately, despite the size of the sample and adequate monitoring its methodological quality has been seriously questioned [26].

Although most of the results of studies performed previously is questioned some authors suggest that the combination therapy is not abandoned, since this scheme can be the most powerful tool in proteinuric nephropathies to cause greater decreases in albumin excretion rate and delay or even prevent progression to end-stage renal disease (ESRD). This type of therapeutic can be important in treating certain conditions since the treatment is individualized [27, 28].

For instance, the combination treatment with ACE inhibitors and ARB inhibitors may have renoprotective additive effects, nevertheless, this seems not to be true in patients with mild renal failure or those with no proteinuria, which may be even harmful for the renal function [29].

Other types of patients with specific associated conditions have been studied for the use of combination therapy with ACE inhibitors and ARB. These conditions are the atherosclerosis and injuries by intra-arterial devices [2]. Studies support the hypothesis that chymase would have an important role in vascular diseases development, since this enzyme is preferably located in the vascular adventitia, while the angiotensin converting enzyme located in the endothelium and intima macrophages. Nowadays it is known that the involvement of the adventitia in vascular injury progression induced by balloon or atherosclerosis is quite significant and that there is an increase in chymase gene expression in atherosclerosis and in injured arteries by ballon [6]. Thus, the addition of an ARB would be beneficial whereas angiotensin II becomes to be produced preferably by the chymase alternative pathway.

The subject has also been discussed in Brazil. A case-control study was conducted with 24 hospitalized patients for heart failure decompensation being treated with ACE inhibitor and in use of dobutamine for more than 15 days. Half of the patients then additionally received ARB and the other half did not. The outcome was the successful on the withdrawal of dobutamine with the combination therapy in heart failure decompensation [30].

The Brazilian guidelines do not recommend the dual blockade of RAAS in general cardiology practice, but only in special situations such as resistant hypertension, nephropathy with significant proteinuria and selected cases of heart failure. In light of current knowledges, rational combinations of each RAAS blocker drugs available with other antihypertensive classes are more recommended [31]. The I positioning of Brazilian Society of Cardiology on resistant arterial hypertension recommends the dual blockade of the renin-angiotensin system just by adding spironolactone as the fourth drug of choice in the treatment of these patients being, therefore, the dual blockade of RAAS an acceptable alternative in that condition [32].

CONCLUSION

It is inferred, therefore, that both angiotensin

converting enzyme inhibitors of angiotensin I as the AT1 receptor blockers of angiotensin II are effective therapeutic strategies to slow the progression of chronic kidney disease on diabetic and non-diabetic proteinuric nephropathy in addition to the importance in the arterial hypertension and heart failure treatment. However, due to the formation of Angiotensin II by alternative pathways, chronic treatment with a single drug inhibitor of RAAS has been questioned. But so far, the data on the double blockade with these drugs are scarce. For more solid conclusions, new more careful approaches should be evaluated by randomized studies in selected patients and individually approached. It is suggested that the combination is not abandoned before prove the effectiveness or ineffectiveness of RAAS double blockade.

ACKNOWLEDGEMENT: None.

CONFLICT OF INTEREST:
The authors declare that they have no conflict of interest.

REFERENCES

1. Sanjuliani A, *et al*. Eixo renin-angiotensin-aldosterone system: physiological and physiopathological bases. *Hospital Universitário Pedro Ernesto*, 10(3), 2011, 34.
2. Resende M, *et al.* Alternative pathways of angiotensin II production and its importance in physiological or physiopathological conditions. *Arquivos Brasileiros de Cardiologia*, 78(4), 2002, 425-31.
3. Becari C, *et al.* Alternative pathways for angiotensin II generation in the cardiovascular system. *Brazilian Journal of Medical and Biological Research*, 44, 2011, 914-919.
4. Taki S, *et al*. Different angiotensin II forming pathways in human and vascular tissues. *Clinica Chimica Acta, Amsterdam*, 305, 2001, 191-195.
5. Takai S, *et al*. New approaches to blockade of the renin-angiotensin-aldosteronesystem:chymase as an important target to prevent organ damage. *Journal of Pharmacological Sciences*, 13, 2010, 301-309.
6. Dagenais GR, *et al*. Angiotensin-converting-enzyme inhibitors in stable vascular disease without left ventricular systolic dysfunction or heart failure: a combined analysis of three trials. *Lancet*, 368, 2006, 581-588.
7. Weinsaf T, *et al*. The Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting–enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *The New England Journal of Medicine*, 342, 2000, 145-153.
8. Cheng MD, *et al*. Effect of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers on all-cause mortality, cardiovascular deaths, and cardiovascular events in patients with diabetes mellitus. *Journal of the American Medical Association*, 174(5), 2011, 773-785.
9. Jorde UP, *et al*. Maximally recommended doses of angiotensin-converting enzyme (ACE) inhibitors do not completely prevent ACE-mediated formation of angiotensin II in chronic heart failure. *Circulation*, 101, 2000, 844-846.
10. Hurtad O, *et al*. Cardiorenal protection during chronic renin–angiotensin–aldosterone system suppression: evidences and caveats. *European Heart Journal - Cardiovascular Pharmacotherapy*, 2015, 126-131.
11. Ferrario CM. Addressing the theoretical and clinical advantages of combination therapy with inhibitors of the renin-angiotensin-aldosterone system: antihypertensive effects and benefits beyond BP control. *Journal Life Sciences*, 86, 2010, 289–299.
12. Locatelli F, *et al*. Inhibition of the renin-angiotensin system in chronic kidney disease: a critical look to single and dual blockade. *Medical and Scientific Publishers*, 113, 2009, 4, 286-293.
13. Fyhrquist F, *et al*. Renin-angiotensin system revisited. *Journal of Internal Medicine, Tomtebodavägen*, 264, 2008, 224-36.
14. Carey RM, *et al.* Role of the angiotensin type 2 receptor in the regulation of blood pressure and renal function. *Hypertension*, 35, 2000, 155-163.
15. Fried F, *et al*. Combined angiotensin inhibition for the treatment of diabetic nephropathy. *The New England Journal of Medicine*, 369, 2013, 1892-190.
16. Maneiro L. Adriana Puente. Renin-angiotensin-aldosterone system blockade in diabetic nephropathy: present evidences. *Journal of Clinical Medicine*, 4(11), 2015, 1908-1937.
17. Jennings DL, *et al*. Combination therapy with an ACE inhibitor and an angiotensin receptor blocker for diabetic nephropathy: a meta-analysis. *Journal Diabetic Medicine, Southampton*, 5, 2007, 486-493.
18. Ontarget, *et al*. Telmisartan, ramipril, or both in patients at high risk for vascular events. *The New England Journal of Medicine*, 358, 2008, 1547–1559.
19. Chen S. Complete inhibition of the renin–angiotensin–aldosterone system: where do we stand? *Current Opinion in Nephrology and Hypertension*, 23(5), 2000, 449–455.
20. Wong J. Is there benefit in dual renin-angiotensin-aldosterone system blockade? No, yes and may be: a guide for the perplexed Diabetes and Vascular Disease Research, Leeds, 10(3), 2013, 193-201.
21. Jafar TH, *et al*. Angiotensin-converting enzyme inhibitors and progression of nondiabetic renal disease. A meta-analysis of patient-level data. *Annals of Internal Medicine*, 135, 2001, 73–87.
22. Sheldon W, *et al*. Cardiovascular and renal outcomes with telmisartan, ramipril, or both in people at high renal risk. Circulation, 123, 2000, 1098-1107.

23. Fried LF, *et al*. Design of combination angiotensin receptor blocker and angiotensin-converting enzyme inhibitor for treatment of diabetic nephropathy (Va Nephron-D). *Clinical Journal of the American Society of Nephrology*, Washington, 4, 2009, 361-368.
24. Gentile G, *et al.* Dual renin-angiotensin system blockade for nephroprotection: still under scrutiny. *Medical and Scientific Publishers*, 129, 2005, 39-41.
25. Nakao N, *et al.* Combination treatment of angiotensin-II receptor blocker and angiotensin-converting-enzyme inhibitor in non-diabetic renal disease (COOPERATE): a randomised controlled trial. *The Lancet*, London, 361, 2003, 117–124, 2003.
26. Kunz R, *et al*. The Cooperate trial: a letter of concern. *Lancet*, 37, 2008, 1575–1576.
27. Rao BP, et al. Dual therapy versus monotherapy oftrandolapril and telmisartan on diabeticnephropathy in experimentally inducedtype 2 diabetes mellitus rats. *Journal of the Renin-Angiotensin-Aldosterone System*, 12(3), 2011, 169–175.
28. Takeyama, Urara M, *et al*. Dual blockade of the rennin–angiotensin system versus maximal recommended dose of angiotensin II receptor blockade in chronic glomerulonephritis. *Clinical and Experimental Nephrology*, 1(12), 2008, 33-40.
29. Lattanzio R, *et al.* Have we fallen off target with concerns surrounding dual RAAS blockade? *Kidney International, Baltimore*, 78, 2010, 539–545.
30. Ochiai ME, *et al*. Addition of angiotensin II receptor blocker in decompensated heart failure. *Arquivos Brasileiros de Cardiologia*, 94, 2010, 2.
31. Campana E. Dual-blockade of the renin-angiotensin-aldosterone system: is there room yet? *Revista Brasileira de Cardiologia*, 2014, 32.
32. Alessi A. *et al*. Authors of the Department of Arterial Hypertension of the Brazilian Society of Cardiology. I *Brazilian positioning on resistant hypertension. Arquivos*, 99, 2012, 22.