

Angiotensin II Antagonists – Clinical Experience in the Treatment of Hypertension, Prevention of Cardiovascular Outcomes and Renal Protection in Diabetic Nephropathy and Proteinuria

revisão

ABSTRACT

Angiotensin II antagonists (AIIAs) were introduced to treat hypertension about 10 years ago. During this period they were evaluated not only in terms of efficacy and safety but also in several large studies with clinical outcomes. They are efficacious in all clinical forms of hypertension and are effective also in all ethnic groups. Cardiovascular and renal protection in proteinuric diabetic nephropathy beyond blood pressure reduction was proved in major clinical studies: Losartan Intervention For Endpoint reduction in hypertension study (LIFE), Reduction of Endpoint in Non-Insulin dependent Diabetes Mellitus with the AII Antagonist Losartan (RENAAL) and Irbesartan Type 2 Diabetic Nephropathy Trial (IDNT). Their blood pressure independent protective effect is also mentioned by the blockade of AT1 receptor. As a class AIIAs have a tolerability profile similar to placebo. (**Arq Bras Endocrinol Metab 2006;50/2:327-333**)

Keywords: Hypertension; Cardiovascular disease; Diabetes mellitus; Angiotensin II antagonists; Stroke; End-stage renal disease; Losartan.

RESUMO

Antagonistas da Angiotensina II – Experiência Clínica com o Tratamento da Hipertensão, Prevenção de Desfechos Cardiovasculares e Proteção Renal na Nefropatia Diabética e Proteinúria.

Os antagonistas da angiotensina II (AIIAs) foram introduzidos para o tratamento da hipertensão arterial há cerca de 10 anos. Durante esse período eles foram avaliados não apenas em termos de eficácia e segurança, mas também em vários estudos grandes com desfechos clínicos. Os AIIAs são eficazes em todas as formas clínicas de hipertensão e, também, em todos os grupos étnicos. Os principais estudos clínicos em pacientes diabéticos com nefropatia e proteinúria comprovaram, além da redução da pressão arterial, proteção cardiovascular e renal: "Losartan Intervention For Endpoint reduction in hypertension study" (LIFE), "Reduction of Endpoint in Non-Insulin dependent Diabetes Mellitus with the AII Antagonist Losartan" (RENAAL) e "Irbesartan Type 2 Diabetic Nephropathy Trial" (IDNT). O seu efeito protetor independente da pressão sanguínea também é mencionado pelo bloqueio do receptor AT1. Os AIIAs, como classe medicamentosa, apresentam um perfil de tolerabilidade semelhante ao placebo. (**Arq Bras Endocrinol Metab 2006;50/2:327-333**)

Descritores: Hipertensão; Doença cardiovascular; Diabetes mellitus; Antagonistas de angiotensina II; Acidente vascular cerebral; Doença renal terminal; Losartana.

ANGIOTENSIN II RECEPTOR ANTAGONISTS (AIIAs) were primarily conceived for the treatment of hypertension. However the cardiovascular benefits of AIIAs have been carefully evaluated not only in terms of their

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*Recebido em 22/12/05
Aceito em 17/01/06*

ability to lower blood pressure in its various clinical forms but also their ability to prevent cardiac events, strokes and target organ damage.

This article reviews the large body of data demonstrating the efficacy of AIIAs in the treatment of hypertension, in the regression of left ventricular hypertrophy and cardiovascular outcomes and in delaying progression of renal failure in patients with type II diabetic nephropathy and proteinuria.

AIIAs as antihypertensive agents

Currently, seven AIIAs are available for the treatment of hypertension (losartan, candesartan, eprosartan, irbesartan, olmesartan, telmisartan, and valsartan) (1-7). And each is available as a fixed-dose combination with a thiazide diuretic. The antihypertensive efficacy of AIIAs has been demonstrated for in mild-to-moderate hypertension as well as severe essential hypertension and isolated systolic hypertension (ISH). AIIAs are also described to be effective in different ethnic populations: Caucasians, Blacks and Asians (8-30).

AIIAs represent an attractive therapeutic option for the management of systolic hypertension, a condition difficult to control in clinical practice (31-33). The ability of AIIAs to impact systolic blood pressure (SBP) is particularly important since systolic hypertension, particularly ISH, represents a powerful risk factor for cardiovascular disease, stroke, and end-stage renal disease (ESRD) and is especially common in elderly individuals (34,35).

Compared with white persons, individuals who are black not only suffer from a greater incidence of hypertension but also tend to have more severe hypertension that is more resistant to effective therapy. Several studies have demonstrated the efficacy of AIIAs in reducing BP in black hypertensive patients (20-22). However there is evidence from a subanalysis of the Losartan Intervention for Endpoint reduction study (LIFE) suggesting that black patients with hypertension and LVH may not respond as favorably as whites in terms of CV outcomes benefits (36).

As a class, AIIAs are generally well tolerated both as monotherapy and in combination with other antihypertensive drugs. The tolerability profile when used in combination regimens is an important consideration given that most patients with hypertension will require administration of multiple agents to adequately control blood pressure. The overall adverse event profile of AIIAs is generally comparable to placebo in randomized clinical trials and superior to that seen with many other types of antihypertensive agents, including calcium channel blockers, ACE inhibitors,

diuretics, and beta blockers (37,38). In a global tolerability assessment of losartan for the treatment of hypertension, the overall adverse event for losartan was similar to that observed for placebo (15.3% vs. 15.5%) (39). Furthermore, the same excellent tolerability profile was observed in special populations of patients such as those with heart failure or renal or hepatic impairment and was uninfluenced by age, race, or gender (39). Similar adverse event profiles have been reported for all AIIAs.

As observed with ACE inhibitors, however, AIIAs may be associated with renal dysfunction in some patients and may give rise to hyperkalemia, especially in those with renal failure or those receiving potassium-sparing diuretics (40). Although angioedema occurs much less frequently in patients receiving AIIA than those receiving ACE inhibitors, it is suggested that AIIAs should be used cautiously in patients with a history of angioedema, particularly that due to the use of ACE inhibitors (41).

Clinical trials with AIIAs in hypertensive patients

The efficacy of an antihypertensive agent must be viewed not only in terms of its efficacy in reducing blood pressure but also in its ability to influence relevant clinical outcomes, like stroke and coronary heart disease (CHD). Several large outcomes studies have been conducted with AIIAs in patients with hypertension: Losartan Intervention For Endpoint reduction in hypertension (LIFE), Valsartan Antihypertensive Long-term Use Evaluation (VALUE), and Study on Cognition and Prognosis in the Elderly (SCOPE) (42-44). The objective of the LIFE study was to compare the losartan-based therapy with atenolol-based therapy, a standard antihypertensive drug with proven CV benefits, on the primary composite endpoint of CV mortality, stroke (fatal and nonfatal), and MI in hypertensive patients (aged 55 to 80 years) with left ventricular hypertrophy (LVH) (42). Compared with an atenolol-based regimen, a losartan-based regimen gave rise to a 13.0% relative risk reduction in the primary composite endpoint of death, MI, or stroke ($p=0.021$), a 24.9% relative risk reduction in fatal or non-fatal stroke ($p=0.001$), and a 25% lower incidence of new-onset diabetes ($p=0.001$). There was no significant difference in CV mortality or MI between the losartan and atenolol groups. Blood pressure fell by 30.2/16.6 mmHg and 29.1/16.8 mmHg in the losartan and atenolol groups, respectively. A lower rate of study drug discontinuation also occurred in the losartan-based group compared with the atenolol-based group (13.1% vs. 18.1%, $p<0.001$).

The LIFE study was sufficiently large to permit evaluation of the impact of losartan on CV events in several subsets of patients, including blacks and those with either diabetes or ISH (45,46). Black patients with hypertension and LVH did not appear to respond as favorably as whites in terms of the primary composite endpoint of cardiovascular death, stroke and MI. In the diabetic hypertensive patients with LVH studied in the LIFE study (n= 1,195) losartan was more effective than atenolol in reducing cardiovascular morbidity and mortality as well as mortality from all causes. In patients with isolated systolic pressure (n= 1,326) the primary composite endpoint was lower in the losartan group than in the atenolol group (11.4% vs. 15.6%, p= 0.06), a difference attributable to stroke but not MI. Total mortality as well as new-onset diabetes were lower in the losartan group.

The results of LIFE are especially important since they indicate for the first time that losartan seems to have benefits beyond blood pressure reduction. The stroke benefits of losartan could potentially have a great impact on public health, especially since stroke occurs with greater frequency than MI in patients with hypertension (47).

The greater cardiovascular benefits of losartan compared with atenolol observed in LIFE have been attributed, in part, to decreases in LVH (48). However, other potential mechanisms may also be involved, including decreased carotid artery hypertrophy (49) and fatty streaks (50), decreased risk of stroke in patients with atrial fibrillation (51), improvement in endothelial function and structure (52), inhibition of thromboxane A₂-dependent platelet aggregation (53), and decreased levels of plasma plasminogen activator inhibitor type-1 antigen (54). A lower incidence of new onset diabetes mellitus in patients receiving losartan compared with atenolol may also have contributed to the overall cardiovascular benefits (see ahead).

SCOPE compared the effects of candesartan with placebo on CV events, cognitive decline, and dementia in elderly hypertensive patients (43). Patients were randomly assigned to receive candesartan or placebo, both in combination with as-needed, open-label, conventional antihypertensive therapy to attain blood pressure goals. In the placebo group, approximately 84% received open-label antihypertensive therapies that included diuretics, ACE inhibitors, beta-blockers, or calcium channel blockers. Although candesartan produced a 27.8% reduction in non-fatal stroke compared with usual antihypertensive treatment, no significant differences were apparent

between candesartan and control groups for the primary endpoint (CV death, non-fatal MI, or non-fatal stroke), for the secondary endpoint measures of all stroke, fatal stroke, MI, cardiovascular mortality, or for the proportion of patients with cognitive decline/dementia. Unlike the LIFE study, however, small differences in blood pressure (3.2/1.6 mmHg) in favor of the candesartan group may have contributed, at least in part, to the stroke benefit seen in patients receiving a candesartan-based therapy.

VALUE investigated the hypothesis that, in hypertensive patients at high risk of cardiac events, valsartan would be more effective than amlodipine in preventing cardiac morbidity and mortality for an equivalent degree of blood pressure lowering (44,55). The study revealed no difference in primary composite endpoint of cardiac morbidity and mortality or in all-cause mortality outcome between the valsartan and amlodipine groups. However, more valsartan patients than amlodipine patients experienced MIs (HR= 1.19, p= 0.02) and fatal and nonfatal strokes (HR= 1.15, p= 0.08). As observed in SCOPE, dissimilarities in achieved blood pressure occurred between the two study groups, a difference that was particularly apparent during the first 6 months of therapy. In fact, at both the beginning and throughout the trial, patients receiving amlodipine had better blood pressure control than those receiving valsartan. For example, more amlodipine-treated patients than valsartan-treated patients achieved the combined systolic/diastolic blood pressure target of < 140/90 mmHg (62% vs. 56%, respectively).

AIIAs and new onset diabetes

Compared with diuretics, beta-blockers, or calcium channel blockers, a consistently lower incidence of type 2 diabetes in hypertensive patients has been observed following treatment not only with AIIAs but also with ACE inhibitors (56). The underlying mechanisms involved in this effect are not fully understood but may involve: improved blood flow to skeletal muscles, thereby, enhancing insulin and glucose delivery to the insulin-sensitive tissues; facilitation of insulin signaling at the cellular level and improved secretion of insulin from the beta cells. The Nateglinide And Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trial and ONGOING Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) are currently ongoing and will provide further information on diabetes prevention by AIIAs as well as their impact on prevention of events and on mortality (57,58).

DIABETIC NEPHROPATHY

Antihypertensive therapy reduces the rate of decline in renal function and delays end-stage renal disease (ESRD) in patients with diabetic nephropathy and, thus, represents a cornerstone of treatment for any diabetic patient with high blood pressure. AIIAs have been shown to consistently produce favorable mortality and morbidity outcomes in endpoint trials in patients with type 2 diabetes and diabetic nephropathy (59,60). Results from the RENAAL and IDNT studies demonstrating that AIIAs delays progression of renal deterioration in patients with clinical diabetic nephropathy and proteinuria will be reviewed. The favorable results in patients with microalbuminuria are presented in other paper of this issue.

RENAAL (59) compared the effects of losartan with placebo (both administered in addition to conventional antihypertensive therapy, including calcium channel blockers, diuretics, alpha-blockers, beta-blockers, and centrally acting agents) in patients with type 2 diabetes and nephropathy, defined as a urinary albumin/creatinine ratio of at least 300 mg/g and serum creatinine between 1.3 to 3.0 mg/dL. The primary endpoint was a composite of the time to first event of doubling of serum creatinine, ESRD, or death, with secondary endpoints of cardiovascular events, progression of renal disease, and changes in proteinuria. Patients treated with losartan demonstrated a 16% reduction ($p=0.02$) in the composite endpoint, a 25% risk reduction in doubling of serum creatinine ($p=0.006$), a 28% reduction in the risk of ESRD ($p=0.002$), and a 20% risk reduction in the composite endpoint of ESRD and death ($p=0.01$), compared with patients receiving placebo. However, losartan was not associated with a significant reduction in the death rate. Losartan-treated patients also experienced a 35% decrease in proteinuria, as shown by a significant fall in the urine albumin/creatinine ratio ($p<0.001$). Losartan did not impact the composite endpoint of CV morbidity or mortality but did reveal evidence of cardioprotection, as evidenced by a 32% reduction in risk of first hospitalization for heart failure ($p=0.005$). Both study groups had similar trough systolic and diastolic blood pressures throughout the study, a finding that indicates that the renoprotective effects of losartan were attributable to effects beyond blood pressure control.

Similar renoprotective effects were obtained with irbesartan in the IDNT study. IDNT (59), which compared irbesartan with amlodipine on the progres-

sion of nephropathy in patients with type 2 diabetes, showed that irbesartan was associated with a lower risk of the primary composite endpoint of doubling of the base-line serum creatinine concentration, the development of ESRD, or death from any cause (20% lower risk vs. placebo, $p=0.02$); 23% lower risk vs. amlodipine, $p=0.006$), a lower risk of doubling of serum creatinine concentration (33% lower risk vs. placebo, $p=0.003$; 37% lower risk vs. amlodipine, $p=0.001$), and a lower relative risk of ESRD although not statistically significant (23% vs. either group, $p=0.07$). The study groups were similar with respect to all-cause mortality and the secondary composite endpoint of cardiovascular events. The serum creatinine concentration also increased more slowly in patients receiving irbesartan (24% more slowly vs. placebo, $p=0.008$; 21% more slowly vs. amlodipine, $p=0.02$). As with RENAAL, the overall benefits favoring AIIA occurred despite the fact that blood pressure control was generally comparable among the study groups. However, mean arterial pressure was significantly higher by 3.3 mmHg in placebo group vs. other two treatment groups ($p=0.001$ for both comparisons), although this did not appear to influence the results after statistical analysis was performed.

Potential mechanisms of renoprotection beyond blood pressure control

In patients with diabetes, AII is believed to play a central role in the progression of renal damage not only through hemodynamic effects but also nonhemodynamic effects, including stimulation of growth factors and cytokines and alterations in extracellular matrix metabolism (61,62). AII gives rise to glomerular hypertension and can alter the filtration properties of the glomerular basement membrane, leading to proteinuria (63,64). AII can also produce glomerular sclerosis via stimulation of transforming growth factor- β , endothelin, and vascular endothelium growth factor and modulation of extracellular matrix (60,61).

In addition to the favorable impact of AIIAs on hypertension and renal hemodynamics, AIIAs may block AII's growth-promoting, profibrotic, nonhemodynamic effects, and this too may contribute to the observed renoprotection. For example, losartan may produce renoprotective benefits by lowering the fibrogenic cytokine TGF- β (64), reducing proteinuria, decreasing renal oxidative stress (65), preserving glomerular and tubulointerstitial structure (66), and reducing the glomerular membrane pore size (62).

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