Therapeutic applications of angiotensin II receptor antagonists

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Applications thérapeutiques des antagonistes récepteurs de l’angiotensine II

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Annales d’endocrinologie, 2000 ; 61, 1 : 47-51

Le système rénine-angiotensine représente aujourd’hui la cible de choix dans le traitement des maladies cardio-vasculaires. Au cours des dernières 30 années plusieurs tentatives d’inhiber l’activité de ce système ont été plus ou moins couronnées de succès. En particulier, l’utilisation des inhibiteurs de l’enzyme de conversion de l’angiotensine II considérablement amélioré le traitement et l’évolution de l’hypertension, de l’insuffisance cardiaque congestive, de la maladie ischémique du myocarde et des néphropathies glomérulaires. D’un autre côté, les inhibiteurs de l’enzyme de conversion ne sont pas sélectivement dirigés vers le système rénine-angiotensine puisqu’ils interfèrent avec un enzyme agissant sur de nombreux substrats différents. De plus, l’inhibition de l’enzyme de conversion n’empêche pas la formation d’angiotensine II par d’autres voies alternatives, si bien que l’inhibition du système rénine-angiotensine demeure souvent incomplète particulièrement lorsque ce système se trouve stimulé dans des conditions pathologiques. Pour toutes ces raisons, le développement d’antagonistes de l’angiotensine II, qui sélectivement inhibe l’action de l’angiotensine II au niveau de son récepteur de sous-type AT1, est singulièrement attractive. Cet article passe en revue les bases physiologiques, les arguments physiopathologiques, ainsi que les applications possibles ainsi que quelques résultats cliniques concernant l’emploi de cette nouvelle classe d’agents.

Therapeutic applications of angiotensin II receptor antagonists

The renin-angiotensin system (RAS) represents today one of the most strategic targets of the therapy of cardiovascular diseases. During the last 30 years a number of more or less successful approaches to inhibit the activity of the RAS have been attempted. In particular, the use of ACE-inhibitors has led to significant improvements in the outcome/treatment of hypertension, congestive heart failure, ischemic heart disease and nephropathies. On the other hand, ACE-inhibitors are not specifically targeted to RAS since they interfere with an enzyme with multiple different substrates. Furthermore, the inhibition of ACE does not prevent the formation of angiotensin II through alternative pathways, and thus the inhibition of RAS is often incomplete, especially under pathologic conditions stimulating RAS. For these reasons, the recent discovery of angiotensin II receptor antagonists, which selectively inhibit the action of angiotensin II at the level of the AT1 subtype receptor, is particularly attractive. This article reviews the background, the rationale and some of the clinical findings and potential applications with this new class of compounds.

THE RENIN-ANGIOTENSIN SYSTEM AS A TARGET OF CARDIOVASCULAR THERAPY

Since its identification, the renin-angiotensin system has been viewed as a fundamental target for development of antihypertensive and cardiovascular therapeutic strategies. Indeed, although the role of angiotensin II (A II) is important in the physiological regulation of blood pressure homeostasis, salt and fluid balance, and possibly tissue growth equilibrium, it is now evident that the biological effects of angiotensin II may contribute to elevate blood pressure and promote progression of target organ disease and deterioration of cardiovascular structure and function [4, 18].

Several different therapeutic approaches based upon interference with the renin-angiotensin cascade and blockade of angiotensin II generation have been developed. Over time renin inhibitors, sympathetic inhibitors, non-selective angiotensin II antagonists and finally angiotensin converting enzyme inhibitors have been tested. Only this latter class of drugs has met the clinical need, in view of the recognized efficacy both in the treatment of hypertension and its sequelae, and in the management of congestive heart failure, ischemic heart disease and nephropathies [3, 5]. On the other hand, ACE-inhibitors are not specifically targeted to the blockade of renin-angiotensin system. In fact they have multiple
enzyme substrates (namely kininase II involved in the degradation of bradykinin). Furthermore, ACE-inhibitors cannot completely inhibit the formation and prevent the escape of angiotensin II during treatment, as repeatedly shown. In fact, alternative enzymatic pathways can generate angiotensin II despite effective ACE-inhibition.

For this reason, since 1975 a number of attempts have been made to design drugs with selective angiotensin II receptor blocking properties [13].

The new class of imidazolic-derivative compounds, collectively defined as the « sartan family » including a number of different molecules (losartan and its metabolite EXP-3174, candesartan cilexetil, irbesartan, valsartan, eprosartan and others), is based on the common property of a selective antagonism for angiotensin II at the AT-1 subtype receptor level. The AT-1 subtype receptor mediates all the principal known effects of angiotensin II, including vasoconstriction, aldosterone stimulation, promotion of thirst and AVP secretion, renal hemodynamic and sodium retention effects, and growth. Therefore, this new class of drugs represents a novel and selective strategy to antagonize the renin-angiotensin system at the biological effector level (binding to receptor, blockade of receptor-coupled cellular mechanisms) which does not seem to interfere with other biological systems (i.e. kinin-kallikrein) [25].

This « sartan compounds » do not cause the common side effects of ACE-inhibitors, such as cough and are characterized by a lack of first-dose hypotensive effect and a more gradual blood pressure lowering effect than ACE-inhibitors, making them very attractive for a well-tolerated treatment of hypertension. For this and other reasons, these drugs have been most recently included among the first-line compounds of choice for the treatment of hypertension in the 1999 WHO/ISH guidelines [26].

This article briefly reviews some of the potential indications of « sartan compounds » for the treatment of cardiovascular and renal disease.

**HYPERTENSION**

In choosing a pharmacologic therapy for hypertensive patients, a number of factors should be carefully considered, including overall efficacy and effects on long-term mortality, compliance, cost, quality of life, concomitant disease/therapies.

The optimal drug formulation chosen to treat hypertension should provide 24-hour efficacy with once-daily dosing. This formulation is preferred because patient adherence to therapy is improved, fewer tablets are usually required (thereby incurring lower costs), hypertension control is smoother and persistent rather than intermittent, and sudden increases in blood pressure are unlikely [23].

The « sartan family » compounds fulfill these criteria since they can be administered once daily, and are very well tolerated.

Randomized studies comparing these compounds with other antihypertensive drugs illustrate the excellent tolerability in hypertensive patients.

In addition, the combination of « sartan » compounds with low-dose hydrochlorothiazide produces significant additional blood pressure lowering effects with no increase in side effects, including metabolic abnormalities.

The excellent tolerability of losartan, for instance, was illustrated in a recent study of long-term safety in open label trials in mild-to-moderate hypertension. As shown in figure 1 during the short-term, double-blind phase of these trials, the number of patients treated with losartan alone or in combination with hydrochlorothiazide who showed clinical drug-related adverse experiences was similar to that observed in the placebo groups [19].

The high tolerability of « sartan compounds » may reveal to be of great importance in the treatment of hypertension. In fact, despite the proven benefits of antihypertensive treatments, such as reductions in the risk of stroke or coronary heart disease, many patients discontinue their antihypertensive medications due to the occurrence of side effects. According to a large UK survey, investigating the discontinuation of antihypertensive therapy, as many as 50% of the patients were no longer taking their initial antihypertensive medications (beta-blockers, ACE-inhibitors, diuretics, or calcium-channel blockers) after six months [14]. Another study by Bloom in USA retrospectively analyzed drug discontinuation rates in about 27,000 patients in the Merck-Medco Managed Care prescription database. This study showed that patients treated with diuretics, beta-blockers, calcium-channel blockers or ACE inhibitors had a prescription persistence ranging...
between 44% and 67% [1]. Interestingly, patients treated with losartan alone or in combination with hydrochlorothiazide had the highest adherence to their medication after one year. Seventy-one percent of patients remained on losartan, a value that was significantly higher than that seen for patients treated with ACE inhibitors (fig. 2).

ACE-inhibitors reduce morbidity and mortality both in patients with chronic heart failure and high-risk patients following acute myocardial infarction (MI) [1, 22, 24]. However the considerable escape from ACE inhibition occurring several months after initiating therapy with ACE-inhibitors, indicated incomplete blockade of AII generation with a return of plasma AII levels and aldosterone to pretreatment levels. This, most likely, occurs because alternative non-ACE pathways are capable of generating AII from angiotensin I (AI) [13].

Unlike the ACE-inhibitors, « sartan compounds » do not produce a rapid decrease in blood pressure following initial administration. This feature represents a definite advantage with respect to safety in the treatment of CHF and post-MI [11].

Several clinical studies clearly show the beneficial acute and chronic hemodynamic and neurohumoral effects of losartan, another compounds of the class, in heart failure patients. The data from the first placebo-controlled, randomized trial of losartan in symptomatic heart failure patients demonstrated that losartan produced a progressive reduction in mean arterial pressure and systemic vascular resistance and a vasodilator response in heart failure patients similar to that observed with ACE-inhibitors. However, in contrast to ACE-inhibitors, losartan produced a dose-dependent increase in AII levels. The rise in plasma AII levels resulting from blockade of AT-1 receptors produces unopposed stimulation of AT-2 receptors with potentially beneficial effects [6, 17].

In symptomatic heart failure patients with impaired left ventricular (LV) function randomized to receive losartan (25 mg to 50 mg once daily) or placebo, beneficial hemodynamic effects on pulmonary capillary wedge pressure, cardiac index and heart rate were observed after 12 weeks of therapy. These data indicate that the selective angiotensin receptors antagonism is associated with sustained, favorable hemodynamic and neurohumoral responses in heart failure patients [6].

Serum creatinine, urea nitrogen, and serum potassium decreased in losartan-treated patients whereas all these values slightly increased in enalapril-treated patients in a study performed on subjects with moderate to severe heart failure. These differences in renal function may be related to the fact that losartan causes vasodilatation of the efferent arterioles by AII antagonism alone, whereas ACE inhibitors produce vasodilation by reducing AII concentrations and by increasing bradykinin concentration, that may contribute to dilate the efferent arterioles to the glomerulus [16].

Two trials have also evaluated the effect of losartan versus placebo on exercise performance. The group receiving losartan therapy showed significant ($p < 0.05$) reductions in the percentage of patients hospitalized for heart failure and all causes of mortality compared with placebo-treated patients.

Finally the Losartan Heart Failure study (ELITE) [20] evaluated the effects of losartan versus captopril added to diuretics for one year in elderly patients with symptomatic heart failure. All-causes hospitalization occurred more frequently on captopril than on losartan, and losartan was associated with improved survival as compared to captopril with a risk reduction of 46% by an intent-to treat analysis. The mechanism by which losartan may have improved survival in ELITE may involve antiarrhythmic effects of losartan or inhibition of norepinephrine release. An unexpected finding of ELITE was the 64% significant reduction ($p = 0.043$) in the risk of sudden cardiac death in losartan treated-patients. Although these findings will be further evaluated in ELITE II, losartan may have possible novel mechanisms of action that may be different from those of ACE-inhibitors and other AII antagonists, such as binding to the tromboxane A-2 receptor and uricosuric effects.

Recent gene knockout studies in mice involving AT-1 receptor blockade have shown a possible role for AT-1 receptor blockade.
receptors in the genesis of ventricular tachycardia when subjected to MI. A subset of patients treated with losartan had reduced QT dispersion. In the ELITE study losartan was better tolerated than captopril, and fewer patients discontinued losartan therapy because of adverse effects. The incidence of cough was significantly (p<0.001) lower in losartan-treated patients (6.5 %) than in patients treated with captopril (17.8 %).

A large trial, ELITE II, is currently under way to specifically compare with a prospective analysis the effects of losartan and captopril on total mortality and sudden death in patients age 60 years or older who have symptomatic heart failure and ejection fractions less than 40 %.

Do we expect the same survival benefit with all angiotensin receptors antagonists? In general, receptor blockers are more dissimilar than enzyme inhibitors such as ACE-inhibitors, and AT-1 receptor antagonists will eventually be subclassified. As other types of AT receptors are identified, we can expect to see different profiles among the various AT-1 receptor blockers.

**RENA L PROTECTION**

The renin-angiotensin system has been implicated in the pathogenesis of renal hemodynamic alterations since the earliest stages of both diabetic and non-diabetic nephropathies. Promising results have been described when Ang II production has been interrupted in hypertensive patients with primary renal disease. These beneficial effects resulting from blockade of the renin-angiotensin system may be a consequence of decrease in intraglomerular pressure or changes in the glomerular basement membrane characteristics. In hypertensive patients with renal disease, the effects of angiotensin receptor antagonists closely resemble those of ACE-inhibitors, which produces renal vasodilatation, and reduces proteinuria.

However, the mechanism of renal protection by ACE-inhibitors may differ from that of angiotensin receptor antagonists. ACE-inhibitors may decrease proteinuria not only by blocking the renin-angiotensin system but also by prolonging the half-life of kinins, which are known to dilate the efferent arteriole, thereby decreasing intraglomerular pressure. However, the renal effects of angiotensin receptor antagonists appear via blockade of AT-1 receptors, and intraglomerular pressure is maintained. This difference in mechanism of action may have important clinical implications particularly in volume-depleted patients.

Preliminary studies in experimental animals models and in patients with non-diabetic renal disease show that the losartan reduces the proteinuria and serum creatinine levels.

The same renal protective effects of losartan in experimental animal models are also demonstrable in patients with non-diabetic renal disease. Ganservoort and colleagues have reported that losartan treatment (50 or 100 mg daily) lowered blood pressure, decreased urinary protein excretion, and elevated renal plasma flow to a degree comparable to that found with ACE-inhibitors [10].

The renal protective effect of losartan has also recently been demonstrated in a double-blind, cross-over study comparing losartan with amlodipine in hypertensive patients with non-diabetic nephropathy. In this study, both losartan and amlodipine significantly lowered blood pressure, but only losartan significantly reduced proteinuria after four weeks [12].

**VASCULAR REMODELING**

Most vascular actions of angiotensin II are mediated through the AT-1 receptors located on vascular smooth muscle and endothelial cells. Vascular hypertrophy, a hallmark of hypertensive vascular injury, may indeed involve AT-1 receptor activation. In contrast, angiotensin II excess resulting from AT antagonism may bind the AT-2 receptor, which is thought to be an antiproliferative receptor [21].

Recent evidence points to a pathophysiologic role for AT II in the development of vascular hypertrophy in the myocardium and in vascular smooth muscle. One novel important mechanism of action through which AT II contributes to vascular structure is its stimulation of ET-1 secretion. In the other hand, binding of AT II to the AT-2 receptors may promote nitric oxide generation and induce apoptosis [9].

**POST-MI SURVIVAL**

After acute MI, approximately 50 % of patients show signs and symptoms of heart failure and approximately 10 % have asymptomatic LV systolic dysfunction. Post-MI patients with heart failure, LV dysfunction, or anterior Q-wave MI have poor prognosis.

Although large clinical trials show that ACE-inhibitors can reduce mortality and cardiovascular events, the prognosis of these high-risk patients is not satisfactory.

The results of ELITE study suggest that losartan may be superior to the ACE-inhibitor captopril in reducing mortality in heart failure patients, primarily by reducing sudden cardiac death.

Since the main cause of death in post-MI patients is sudden cardiac death, which is modestly affected by ACE-inhibitors, angiotensin II receptors antagonists may reduce mortality in these patients more effectively than ACE-inhibitors.
THERAPEUTIC PERSPECTIVES

Future clinical trials on antihypertensive therapy should address a number of issues including: mortality and morbidity evaluation by endpoint analysis, quality of life and tolerability, assessment of efficacy in special subgroups stratified by age, sex, presence of co-morbidity (diabetes, obesity etc), and definition of optimal target blood pressure for subgroups at particular risk.

A number of large-scale survival trials with angiotensin antagonists and in particular with losartan are currently ongoing and involving more than 30,000 patients. These trials include the LIFE, a study on left ventricular hypertrophy and associated prognosis in hypertension [7], the Losartan Heart Failure Survival Study (ELITE II), Losartan Post-MI Survival Study (OPTIMAAL) [8], and Losartan Renal Protection Study (RENAAL).

In particular OPTIMAAL will include approximately 5,000 high-risk post-MI patients, that is patients with symptomatic heart failure, LV systolic dysfunction, and/or Q-wave anterior MI. The study will compare the effects of losartan and captopril on sudden cardiac death/resuscitated cardiac arrest, cardiovascular death, death from progressive heart failure, hospitalization for heart failure, hospitalization for any cause, and stroke. Clinically stable patients will be randomized to receive losartan (50 mg once daily) or captopril (50 mg three times daily) within 10 days of MI.

REFERENCES