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Scientific Update™

The Role of Angiotensin II AT_1 Receptor Blockers in Congestive Heart Failure and LVH

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Angiotensin-converting enzyme inhibitors (ACEI) have had a major impact on the therapy of congestive heart failure, improving symptomatic control and prolonging survival. The potential beneficial effects of ACE inhibition result from vasodilation, decreased adrenergic drive and positive effects on ventricular and vascular remodelling. However, inhibitors of the angiotensin-converting enzyme may not be sufficient to fully block the renin angiotensin system. There is evidence that other enzymes such as chymases can result in activation of angiotensin I to angiotensin II in the myocardium and other tissues. There is also evidence of partial escape from ACEI during prolonged therapy. The addition of an angiotensin receptor blocker may result in a more complete blockade of the renin angiotensin system and, therefore, more clinical benefits (Figure 1). The present report summarizes several papers presented at the recent American College of Cardiology meeting which examined this hypothesis.

Irbesartan and conventional heart failure therapy

In a report presented at the ACC, irbesartan was studied in combination with conventional therapy, including ACE inhibitors, in patients with mild-to-moderate heart failure.[1] Irbesartan is a new angiotensin II AT_1 receptor blocker that has been shown to be effective in hypertension; it has a half-life of 11-15 hours resulting in sustained inhibition of the renin-angiotensin system. The primary objective of this study was to estimate changes in exercise tolerance achieved by adding irbesartan to conventional heart failure therapy including ACE inhibitors, for periods of 12 weeks. Secondary objectives included changes in left ventricular ejection fraction, clinical status (NYHA Class) and in circulating levels of neurohormones in a substudy.

Patients with NYHA Class II to III symptoms were enrolled in this study if their LV ejection fractions were ≤40% and they demonstrated exercise tolerance between 2-12 minutes on a modified Naughton exercise test. They were also required to be on stable ACEI for ≥6 weeks. Following a single-blind conventional heart failure therapy lead-in phase in which exercise tolerance was evaluated, patients were ran-

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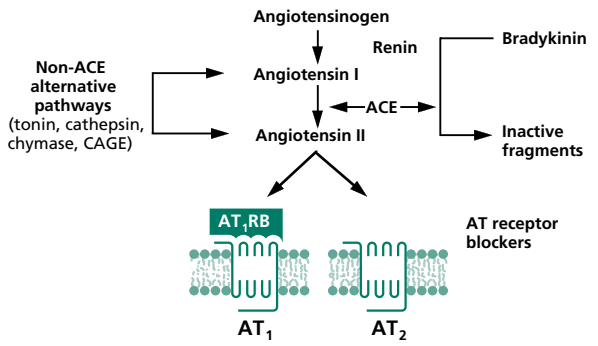
Figure 1: The renin-angiotensin system and AT_1 blockade



Johnston et al. 1997[2]

domized to treatment with irbesartan plus conventional therapy (57 patients) or remained on conventional heart failure therapy alone (52 patients). Irbesartan was started at a dose of 12.5 mg and titrated to the usual starting dose of 150 mg as tolerated. Of the 145 patients enrolled, 109 were randomized and 97 completed the study. Baseline characteristics were balanced between the groups. There was a male predominance and most patients demonstrated NYHA Class II heart failure and reduced ejection fraction.

Exercise time showed a tendency to increase in the irbesartan group by 63.5 seconds, compared to 41 seconds in the conventional therapy group. These changes were not significant, however, as the study was underpowered to demonstrate significant changes in the primary endpoint. Nevertheless, 85% of the irbesartan patients demonstrated an improvement in exercise tolerance compared to 70% of the non-irbesartan treated group.

There was also a tendency for a greater increase in left ventricular ejection fraction in irbesartan-treated patients (4.4 units vs. 2.6 units). As expected, increases in plasma renin and angiotensin II were greater in the irbesartan group, however, increases in aldosterone were greater in the placebo group. The conventional therapy group also showed a slight increase in systolic and diastolic blood pressure, whereas blood pressure decreased in irbesartan-treated patients with only small increases in heart rate. While there were no deaths in the study, 21% of conventionally treated patients — compared with 12% of irbesartan patients — had at least one cardiac event. Most of these were accounted for by increased diuretic use in the non-irbesartan treated patients.

This study demonstrated that irbesartan, in combination with an ACE inhibitor based regimen, was well tolerated. There were no significant differences in adverse events between the two groups. In patients with mild-to-moderate heart failure, therefore, the addition of irbesartan to conventional heart failure therapy, including ACE inhibitors, is safe and tends to increase exercise tolerance. It also results in a slight improvement in hemodynamics.

Angiotensin II AT_1 receptor blockers compared with ACEI

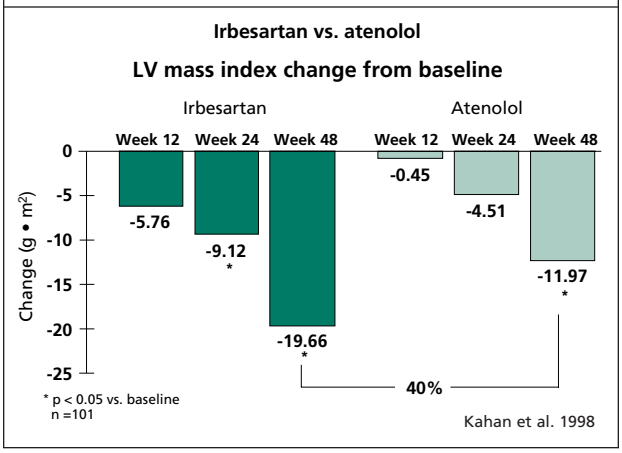
Although the above study lacked the statistical power to demonstrate a significant difference in the primary endpoint, a beneficial effect of angiotensin II AT_1 receptor blockers on exercise tolerance in patients with heart failure is supported by another study presented at the American College of Cardiology meeting.[3] Vijay et al compared irbesartan with the ACEI lisinopril in patients with mild to moderate heart failure. They randomized 134 patients with symptomatic heart failure and reduced left ventricular ejection fraction (<40%). All patients were on stable doses of diuretics and ACEI prior to being randomized to treatment with either the angiotensin II AT_1 receptor blocker irbesartan or the ACEI lisinopril, titrated to 150 mg or 20 mg per day, respectively. After 12 weeks of treatment, both therapies resulted in significant increases in exercise duration by modified Naughton protocol (+72.5 and +65 seconds respectively). Irbesartan and lisinopril were similarly well tolerated

and both resulted in small but non-significant changes in ejection fraction.

In another study presented at the ACC, angiotensin II AT_1 receptor blockade was combined with ACE-inhibition in the treatment of congestive heart failure (CHF).[4] The hypothesis tested was that adding an angiotensin II AT_1 receptor blocker (losartan) to ACEI in patients with heart failure improves left ventricular systolic function both at rest and during exercise. 73 patients with background stable doses of ACE inhibitors and diuretics were randomized to either placebo or losartan. All had ejection fractions <40%. Exercise tolerance was determined by bicycle ergometry under continuous ECG surveillance. Patients were studied in the supine position and ventricular volume and function were determined during exercise by continuous echocardiography. 42 patients were randomized to losartan, while 51 patients received placebo treatment. Baseline characteristics were comparable between the groups including the type and dosage of ACE inhibitor used and LV function (LVEF 24% in both groups).

Treatment with losartan, in addition to ACE inhibitor, was well tolerated, with only three patients complaining of dizziness (compared to two in the placebo arm) and two experiencing worsening heart failure (one in the placebo arm). Patients treated with losartan and an ACE inhibitor showed a significant increase in resting left ventricular ejection fraction and decreases in end diastolic and end systolic volumes. There was a similar trend seen in the placebo group but this did not achieve significance. Exercise duration was increased to 621 versus 370 seconds, and ejection fraction increased significantly in the losartan group during exercise. These results show that an angiotensin II AT_1 receptor blocker is well tolerated when added to an ACE inhibitor in patients with heart failure and that this combination improves functional capacity and indices of left ventricular function at rest and during exercise.

Figure 2: Rate and extent of left ventricular hypertrophy regression



Irbesartan versus beta-blockade in LVH

A fourth study compared treatment with angiotensin II (AT_1) blockade with irbesartan and beta-blockade on the rate and extent of regression of left ventricular hypertrophy (LVH). Angiotensin II (AII) plays an important role in the development of left ventricular hypertrophy and this carries important prognostic information.[5] Patients with normal left ventricular geometry are at the lowest risk, but their risk of cardiovascular events increases progressively with remodelling, both for exentric and concentric ventricular hypertrophy. As well, there is evidence that reversible LVH improves prognosis. It was hypothesized that angiotensin II AT_1 receptor blockers could be used to assess the role of angiotensin II in LVH.

The primary objective of this study was to compare changes in left ventricular mass index after 24 weeks of treatment with irbesartan as compared with atenolol. The secondary objective was to compare changes in left ventricular mass index at 48 weeks, systolic ventricular function, diastolic function and levels of neurohormones.

The study population consisted of patients with LVH (≥131 gm^2 for men, 100 gm^2 for women) and mild-to-moderate hypertension. 155 patients were enrolled with a mean

age of 54; 68% were male. The protocol consisted of a four-week, single-blind, placebo run-in phase prior to randomization. Dose escalation occurred at 12 weeks and felodipine was added if diastolic blood pressure exceeded 90 mm Hg. Irbesartan and atenolol were equally effective at reducing systemic blood pressure.

Systolic blood pressure was normalized in three-quarters of the patients in both treatment groups. Irbesartan resulted in a decrease in left ventricular mass index which was progressive over 48 weeks and achieved statistical significance at 24 weeks. Atenolol decreased the left ventricular mass index to a lesser extent and this was not significant at 24 weeks, achieving statistical significance only at 48 weeks (Figure 2). Left ventricular systolic function was normal at randomization, however, 85% of patients had evidence of diastolic dysfunction. Both treatments significantly improved diastolic dysfunction, although atenolol did this to a greater extent. While both treatments were well tolerated, patients treated with irbesartan experienced fewer side effects, and in particular, less bradycardia and fatigue.

Treatment with irbesartan or atenolol resulted in similar decreases in blood pressure, however, irbesartan significantly decreased the left ventricular mass index at 24 weeks (primary endpoint). In contrast, treatment with atenolol only achieved a significant decrease in mass index at 48 weeks, consistent with a greater effect of irbesartan on LVH. These results support an important role of angiotensin II AT_1 receptor blockers in the treatment of LVH.

Conclusion

Contemporary treatment of CHF includes prevention of continuing damage to the myocardium, the relief of symptoms of congestion, and reduction in mortality. In addition to playing a key role in heart failure, angiotensin contributes to the pathogenesis of hypertension, arterial disease, cardiac hypertrophy, and diabetic renal disease.

The addition of angiotensin II AT_1 receptor antagonists to conventional ACE inhibition may provide additional benefits in the treatment of heart failure and left ventricular hypertrophy and may offer unique opportunities in combatting the functional and structural alterations that result from the neurohumoral activation. This combination appears to be well tolerated and to provide distinct advantages over ACE inhibition alone. In addition, this group of agents, as demonstrated with irbesartan, appears to be more effective than other antihypertensives such as beta-blockers in reducing left ventricular hypertrophy, while offering comparable blood pressure lowering efficacy.

Further studies are needed to address the clinical benefits of angiotensin II AT_1 receptor blockers and to define their role in treating structural and functional abnormalities in patients with heart failure or hypertension.

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