Clinical Differences among Angiotensin II Receptor Antagonists

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The six major classes of antihypertensive agents prescribed worldwide are similar in efficacy but dissimilar in tolerability. Recently, the World Health Organization-International Society of Hypertension (WHO-ISH) concluded that agents from all six classes are suitable for the initiation and maintenance of antihypertensive therapy, including the newest class of agents, the angiotensin II receptor antagonists (AIIRAs). The ideal antihypertensive agent should be effective and well tolerated, as well as synergistic in blood pressure-lowering effects when combined with other agents. As monotherapy, AIIRAs have demonstrated efficacy similar to other classes of antihypertensive agents in numerous clinical trials. Several AIIRAs have also demonstrated enhanced efficacy when combined with a low dose of the diuretic hydrochlorothiazide (HCTZ). A well-known feature of this new class of agents is placebo-level tolerability; however, less is known about intra-class differences. Losartan, the first approved AIIRA, has become an important benchmark for within-class comparisons with respect to antihypertensive efficacy. Head-to-head comparisons between losartan and newer AIIRAs have been conducted; their cumulative results indicate that the antihypertensive effect and antagonistic activity of losartan may be the weakest among AIIRAs. In a recent clinical trial, we demonstrated that irbesartan produces statistically superior blood pressure reduction when compared to valsartan. This may have clinical implications for agent selection among the AIIRAs. *Key words: angiotensin II receptor antagonist, hypertension, irbesartan, tolerability, valsartan.*

BACKGROUND

In 1993 and again in 1997, the Joint National Committee on the Detection, Evaluation, and Treatment of High Blood Pressure recommended initiating antihypertensive therapy with a diuretic or beta-blocker, since data from numerous randomized, controlled trials had demonstrated a decrease in morbidity and mortality with these agents [1, 2]. In 1993, the World Health Organization–International Society of Hypertension (WHO-ISH) took a different position, stating that the benefit derived from a specific class of antihypertensive agents was less important than the general benefit of lowering blood pressure. They suggested that physicians could select from all five major classes of agents available at that time [3]. In its 1999 version, the WHO-ISH included the sixth class of agents—angiotensin II receptor antagonists (AIIRAs)—among the initial choices for treatment of hypertension [4].

AIIRA agents are currently prescribed for the treatment of hypertension as monotherapy or in combination with other agents. As a class, AIIRAs have demonstrated efficacy similar to other classes of antihypertensive agents, including diuretics, calcium antagonists, beta-blockers and angiotensin-converting enzyme (ACE) inhibitors [5–9]. Ongoing long-term studies will help answer the question of whether AIIRAs provide additional benefits in preventing or reversing end-organ damage and reducing morbidity and mortality attributable to hypertension [10]. When choosing an AIIRA agent, it is important to note that there are intra-class differences.

SELECTION OF ANTIHYPERTENSIVE AGENT

The choice of antihypertensive therapy should be individualized, based on a number of factors, including the degree of blood pressure elevation, existence of co-morbid conditions, presence of risk factors for target organ damage, as well as profile because of its impact on patient adherence and treatment [1–4].

Benefits of blood pressure reduction

The earliest data demonstrating significant reductions in cardiovascular outcomes with blood pressure reduction involved diuretic or beta-blocker regimens [11]. Later trials showed similar benefits with calcium antagonists and ACE inhibitors. The Systolic Hypertension in Europe (Syst-Eur) trial ($n = 4695$) demonstrated that, compared to placebo, antihypertensive therapy initiated with the calcium antagonist nitrendipine reduced the risk of cardiovascular complications in patients who were ≥ 60 years of age and had systolic hypertension [12]. The Captopril Prevention Project (CAPPP) randomized nearly 11 000 patients <66 years of age to either conventional

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treatment (diuretics, beta-blockers) or the ACE inhibitor captopril and found no difference between the two treatments in preventing cardiovascular morbidity and mortality [13]. Captopril was also found to be as effective as the beta-blocker atenolol in reducing the incidence of diabetic complications in type 2 diabetics in the United Kingdom Prospective Diabetes Study (UKPDS) [14]. Recently, the Swedish Trial in Old Patients with Hypertension-2 (STOP-Hypertension-2) study strengthened the conclusion that the benefit of antihypertensive treatment derives largely from the overall blood pressure-lowering effect. The trial randomized over 6600 patients aged 70–84 years to either conventional therapy (beta-blockers and diuretics) or newer agents (ACE inhibitors and calcium antagonists). Blood pressure was reduced similarly in all groups, and conventional and newer agents provided similar benefits in preventing cardiovascular events and mortality [15].

Achieving blood pressure goals

In most of the large hypertension studies, a relationship was found between the degree of benefit and the degree of diastolic blood pressure reduction achieved down to 90 mmHg [16]. There is also evidence that the degree of benefit correlates with the degree of systolic blood pressure reduction induced by treatment [17]. Whether the diastolic blood pressure reduction to <90 mmHg also relates in a continuous fashion with treatment benefits is still somewhat uncertain. The Hypertension Optimal Treatment (HOT) study suggests that this may be the case and evidence is available that reducing diastolic blood pressure well below 90 mmHg and even 80 mmHg may be more beneficial in diabetic patients and patients with renal damage and proteinuria [18]. In most trials, achieving blood pressure control has not been possible with monotherapy in the majority of patients. In the HOT study, for example, on-treatment diastolic blood pressure was reduced to 83 mmHg, but this required combination of two drugs in about two-thirds of the patients. Combination-treatment is also common in diabetic patients if diastolic blood pressure well below 90 mmHg has to be achieved.

Drugs used in combination therapy need to be good partners. The combination of agents should produce a synergistic effect and be well tolerated. The 1999 WHO-ISH guidelines recommend the use of combination therapy with additive effects, i.e. the combination should deliver blood pressure reduction about twice as great as that obtained with a single drug. The guidelines note that AIIRAs and diuretics are an effective drug combination [4].

Patient compliance with the treatment regimen is a critical issue and is related to the tolerability of medications. When side-effects emerge, many patients stop taking their medicine; hence a favorable tolerance profile is a valuable feature for an antihypertensive agent. AIIRAs have demonstrated a class-wide tolerability profile similar to placebo at all doses. A review of recent studies focusing on the discontinuation of initial antihypertensive medications found that after 6 months, fewer than 50% of patients continued to take their initially prescribed agent, regardless of class. However, a higher percentage of patients continued to take the AIIRA losartan than ACE inhibitors after 12 months of treatment [19]. Another study found that patients were more likely to continue on AIIRAs than other classes of agents. In a retrospective analysis of the refill behavior of patients who had recently started outpatient antihypertensive therapy, researchers found that the percentage of patients continuing initial AIIRA therapy was substantially higher at the 12-month follow-up period than the percentage who continued therapy with ACE inhibitors, calcium antagonists, beta-blockers or thiazide diuretics (64% vs 58, 50, 43 and 38%, respectively) [20].

Preventing target organ damage

The ultimate purpose of lowering blood pressure is to protect against cardiovascular and renal disease and their consequences. Angiotensin II (Ang II) activity is involved in the pathogenesis of hypertension and may be implicated in both cardiac and renal damage. Hypertensive patients are frequently found to have left ventricular hypertrophy, carotid artery stenosis or wall thickening, microalbuminuria, or other sub-clinical manifestations of target organ damage.

ACE inhibitors have proven beneficial in patients with congestive heart failure [21]. They have also been shown to protect the kidney, in patients with diabetic and nondiabetic nephropathy. Finally, the Heart Outcomes Prevention Evaluation (HOPE) study proved that in high risk normotensive patients or in hypertensive patients with blood pressure control by treatment the ACE inhibitor ramipril reduced the rates of death, myocardial infarction and stroke for patients at high risk for cardiovascular events, when compared to placebo [22]. There is therefore conclusive evidence that blocking the renin-angiotensin system (RAS) has a protective effect on a variety of organs in a variety of diseases.

The two classes of agents that block the action of Ang II, ACE inhibitors and AIIRAs, do so by different mechanisms. ACE inhibitors block the enzyme that converts angiotensin I into Ang II, while the AIIRAs selectively block one of the two main Ang II receptors—subtype AT_1. The AIIRA class may have a distinct clinical advantage over ACE inhibitors, which often produce the unpleasant side-effect of cough [23, 24]. It is

proposed that this occurs because bradykinin is also inhibited, and that it accumulates. In contrast to ACE inhibition, blocking the AT_1 receptor also blocks Ang II, which may be produced through non-ACE mechanisms. By blocking the receptor believed to be responsible for the deleterious effects of Ang II, AIIRAs may also potentially be of special benefit in the treatment of diabetic nephropathy and heart failure. At present, it is not known if AIIRAs will demonstrate a prominent ability to lower cardiovascular and renal morbidity and mortality. There are currently several large clinical trials in progress evaluating this potential benefit [10, 25].

DIFFERENCES WITHIN THE CLASS OF AIIRA AGENTS

There are six currently approved AIIRA agents—candesartan, eprosartan, irbesartan, losartan, telmisartan and valsartan. Although it is too early to say whether there are differences within the class of AIIRA agents in regards to target organ protection—such studies are underway but will take several years to complete—there are differences in the efficacy of blood pressure reduction within the class. For example, in contrast to irbesartan and candesartan, which exhibit greater efficacy at higher doses [26, 27], losartan does not appear to exhibit a clear dose–response effect in blood pressure reduction [28]. Data are somewhat conflicting regarding the dose–effect relationship for valsartan [29, 30]. Direct comparison trials have also been performed, showing differences in pharmacodynamic and pharmacokinetic effects [31]; Belz describes these in a separate article in this supplement.

Losartan, the first approved AIIRA, has become an important benchmark for intra-class comparisons of efficacy in blood pressure reduction. Placebo-controlled, double-blind, comparator trials conducted with losartan and the newer AIIRAs indicate that the antihypertensive effect and antagonistic activity of losartan may be the weakest in the AIIRA class. Thus far, three of the newer AIIRAs—irbesartan, candesartan and valsartan—have demonstrated superior efficacy compared to the maximum dose of losartan (100 mg qd) [32–34]. Furthermore, irbesartan and candesartan have each surpassed losartan in efficacy in two independent trials [32, 33, 35, 36]. However, data from two more recently published clinical trials found equivalent efficacy when losartan was compared to candesartan or valsartan. In one of these trials, losartan and candesartan were compared, and found to be equivalent, at initial doses of 50 and 8 mg, respectively, or at titrated doses of 100 and 16 mg, respectively [37]. In the other trial, equivalent efficacy was reported for losartan 50 mg and valsartan 80 mg [38]. Clinical studies comparing telmisartan and eprosartan have also demonstrated superior efficacy in blood pressure reduction compared with losartan 50 mg [39–41].

Thus, as indicated by the results of head-to-head comparator studies, the AIIRAs developed subsequent to the approval of losartan are at least equivalent, and probably more efficacious, than this "benchmark" drug. This is the case, for irbesartan is the only AIIRA that indeed has demonstrated clinical superiority in blood pressure reduction against two distinct AIIRAs. The first was losartan, as previously noted. A recently published study adds to the knowledge base of AIIRA intra-class differences by providing new information on the superiority of irbesartan compared to a second AIIRA, valsartan.

It should be noted that some trials use office blood pressure measurements, while others use 24-h ambulatory blood pressure (ABP) monitoring. Studies based on ABP measurements have distinct advantages in clinical studies. ABP monitoring has greater reproducibility than office measurements and can evaluate mean 24-h, daytime and night-time blood pressure values for an individual or within a group of individuals [42, 43]. Because ABP provides information about the antihypertensive effect of an agent over the 24-h period, it is more reflective of the "daily-life" blood pressure of the patient.

IRBESARTAN VS VALSARTAN

Irbesartan is a potent AIIRA that provides highly selective, insurmountable, long-lasting, dose-related blockade of the AT_1 receptor [44–46]. Long-term efficacy with irbesartan treatment as monotherapy and in combination with hydrochlorothiazide (HCTZ) was demonstrated in an analysis of five multicenter, open-label studies in which 83% of all patients maintained blood pressure normalization at 12 months [47]. Valsartan is a potent, orally active, highly selective AT_1 competitive receptor antagonist [48–50]. It differs from irbesartan in its half-life and oral bioavailability (11–15 h and 60–80% for irbesartan vs 6 h and 10–35% for valsartan) [44, 49]. When the Ang II antagonistic effects of three AIIRAs were compared, the following rank order of antagonistic intensity was demonstrated: irbesartan > valsartan > losartan [29]. We conducted the first direct clinical comparison trial to determine if irbesartan's superior blockade of Ang II is associated with greater antihypertensive efficacy than valsartan [51, 52].

Objectives and methods

The patients enrolled in the study had mild-to-moderate hypertension and were mostly white and male (96% and 65%, respectively), with a mean age of 55 years. Following a placebo run-in period, patients were randomized in a double-blind fashion to either irbesartan

(150 mg; $n = 211$) or valsartan (80 mg; $n = 215$) for 8 weeks. Patients were monitored by ABP office blood pressure at trough and self measured home blood pressure (morning and evening measurements). The primary endpoint was change in ambulatory diastolic blood pressure (ADBP) at trough. Trough BP was assessed by multiple automatic measurements performed at the 24-h after dose.

Results

Irbesartan reduced mean trough ADBP at week 8 by 1.9 mmHg more than valsartan (−6.7 vs −4.8 mmHg). Similarly, irbesartan produced a 4.1-mmHg greater reduction in trough ambulatory systolic blood pressure than did valsartan (−11.6 vs −7.5 mmHg; $p < 0.01$). Statistically significant reductions in favor of irbesartan vs valsartan were also observed for mean 24-h systolic and diastolic blood pressures (−10.2/−6.4 vs −7.8/−4.8 mmHg, respectively; $p < 0.01$). Irbesartan reduced daytime and morning self-measured blood pressure at home more than valsartan, whereas the reduction in nighttime and evening home blood pressure was similar in the two groups. There were statistically significant reductions in favor of irbesartan vs valsartan for office-measured trough systolic and diastolic blood pressure. The percentage of patients who attained office blood pressure normalization (52.5% vs 38.2%) or response (63.9% vs 44.3%) was significantly higher for irbesartan than valsartan. Both irbesartan and valsartan were well tolerated, with similar safety profiles.

CONCLUSIONS

AIIRAs have secured a role in the treatment of hypertension and should be considered for initial, maintenance or combination therapy. The antihypertensive efficacy of drugs belonging to this class is not the same, however in a recently published study comparing the efficacy of irbesartan with valsartan, we have extended the available data demonstrating intra-class differences among AIIRA agents. Irbesartan has demonstrated statistically superior blood pressure reduction and control rates as compared to valsartan. These results are similar to those obtained in comparisons of irbesartan and losartan and may be due to the significantly greater antagonism of Ang II previously demonstrated with irbesartan as compared with valsartan and losartan. Soon we will know if these differences translate into improvements in cardiovascular and renal morbidity and mortality.

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