R E V I E W

Long-term use and tolerability of irbesartan for control of hypertension

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Abstract: In this review, we discuss the pharmacological and clinical properties of irbesartan, a noncompetitive angiotensin II receptor type 1 antagonist, successfully used for more than a decade in the treatment of essential hypertension. Irbesartan exerts its antihypertensive effect through an inhibitory effect on the pressure response to angiotensin II. Irbesartan 150–300 mg once daily confers a lasting effect over 24 hours, and its antihypertensive efficacy is further enhanced by the coadministration of hydrochlorothiazide. Additionally and partially beyond its blood pressure-lowering effect, irbesartan reduces left ventricular hypertrophy, favors right atrial remodeling in atrial fibrillation, and increases the likelihood of maintenance of sinus rhythm after cardioversion in atrial fibrillation. In addition, the renoprotective effects of irbesartan are well documented in the early and later stages of renal disease in type 2 diabetics. Furthermore, both the therapeutic effectiveness and the placebo-like side effect profile contribute to a high adherence rate to the drug. Currently, irbesartan in monotherapy or combination therapy with hydrochlorothiazide represent a rationale pharmacologic approach for arterial hypertension and early-stage and late-stage diabetic nephropathy in hypertensive type II diabetics.

Keywords: AT1 receptor blockers, renin-angiotensin-aldosterone system, heart, renal, arterial, hypertension

Introduction

The renin-angiotensin-aldosterone system plays a pivotal role in the regulation of blood pressure and body sodium and water homeostasis. The renin-angiotensin-aldosterone system is implicated in the pathogenesis and progression of numerous cardiovascular and renal pathologies, including hypertension, structural cardiac remodeling, myocardial infarction, heart failure, and chronic kidney disease.[1,2] The inhibition of the renin-angiotensin-aldosterone system is therefore a therapeutic target.

In our pharmacological arsenal, we currently have four weapons that inhibit the renin-angiotensin-aldosterone system through either direct or complementary mechanisms. Angiotensin-converting enzyme inhibitors block the conversion of angiotensin I to angiotensin II; angiotensin receptor blockers selectively antagonize angiotensin II at the AT1 receptors; aldosterone receptor blockers reduce the effects of aldosterone; and renin inhibitors, the newest drug group, directly inhibit human renin.

Angiotensin receptor blockers have been available for management of hypertension for almost 20 years. So far, seven angiotensin receptor blockers have been approved by the US Food and Drug Administration, with slightly different therapeutic indications (Table 1). In comparison with angiotensin-converting enzyme inhibitors, angiotensin receptor blockers have very similar antihypertensive efficacy, but a better

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side effect profile, mainly because they are not associated with cough, a major side effect of ACE inhibitors.[3,4] Several angiotensin receptor blockers have a long plasma half-life and binding time to the AT1 receptor, enabling a once a day administration. Because the side effect profile of drugs and the complexity of dosage regimens are known to have the greatest impact on patient adherence, angiotensin receptor blockers have an ideal profile, with a placebo-like tolerability and pharmacokinetic properties allowing a once-daily dosing regimen.[5]

Irbesartan (Aprovel®, Avapro®, Irbetan®, Karvea®) is a well established angiotensin receptor blocker, approved worldwide for the treatment of hypertension. In essential hypertension, irbesartan lowers blood pressure over 24 hours. The usual starting dosage is 150 mg once daily, but the dose can be uptitrated to 300 mg once daily if necessary.[6] In many countries (US, Canada, Europe), irbesartan is also approved for the treatment of nephropathy in patients with hypertension

and type 2 diabetes mellitus. In the latter indication, 300 mg once daily is the recommended maintenance dosage.[6]

This review summarizes the pharmacokinetic and pharmacodynamic characteristics of irbesartan, with a particular focus on recent clinical evidence about the therapeutic efficacy and tolerability of irbesartan when used as oral monotherapy or combination therapy in essential hypertension, diabetic nephropathy, and cardiac disease.

Overview of pharmacology
Irbesartan is an imidazole derivative with a bipentyl-tetrazole side chain. It does not require biotransformation to exert its pharmacological action. The molecule has a high affinity for the AT1 receptor in human vascular smooth muscle cells, inducing in vitro a rightward shift of the angiotensin II concentration-response curve and a depression of the maximal response to angiotensin II characteristic of insurmountable blockade of AT1 receptors.[7] Following oral administration,

Table 1 Indications of the seven approved angiotensin receptor blocker (listed in order of date of appearance on the market)[89,90]

	Essential hypertension	Heart failure	Cardiovascular prevention	Nephropathy
Losartan	X	X Symptomatic NYHA II–III[a]	X ↓ stroke risk in LVH	X Hypertensive, type II diabetics (↑ creatinine and/or albuminuria ≥300 mg/day)
Valsartan	X	X Symptomatic NYHA II–III[b] X Asymptomatic if recent MI and LVEF ≤ 40%		
Candesartan	X	X If LVEF ≤ 40%[a]		
Irbesartan	X			X Hypertensive, type II diabetics, (↑ creatinine and/or albuminuria ≥30 mg/day)
Olmesartan	X			
Telmisartan	X		X ↓ MI and stroke risk in high CV risk and/or diabetic patients with target organ damage	
Eprosartan	X			

Notes: [a]As add-on therapy to angiotensin-converting enzyme inhibitors or as an alternative to angiotensin-converting enzyme inhibitors in patients unable to tolerate angiotensin-converting enzyme inhibitors; [b]As add-on therapy to angiotensin-converting enzyme inhibitors when beta-blockers cannot be used or as an alternative to angiotensin-converting enzyme inhibitors in patients unable to tolerate angiotensin-converting enzyme inhibitors; ↓ indicates decrease.
Abbreviations: ARB, angiotensin receptor blocker; ACE-I, ACE inhibitor; LVEF, left ventricular ejection fraction; CV, cardiovascular; MI, myocardial infarction; LVH, left ventricular hypertrophy.

the absolute average bioavailability is high (60%–80%), the highest in its class, and is not affected by concomitant food intake.[8] In healthy subjects, peak plasma concentration and the area under the curve are dose-dependent, whereas the time to peak plasma concentration is dose-independent (1.5–2.0 hours). Steady-state plasma concentrations are reached after three days of once-daily administration, with an elimination half-life of about 11–15 hours, and no evidence of accumulation over one-week multiple dosing.[9] The degree of plasma protein binding is ≥90%.[10] Irbesartan is strongly metabolized via hepatic glucuronidation and oxidation (mainly by the cytochrome P450 2C9 isoenzyme) and excreted by both biliary (80%) and renal (20%) routes. No active metabolites have been identified. No gender-related or age-related dosage adjustment is necessary, not even for patients with mild-to-moderate hepatic insufficiency, heart failure, or renal insufficiency.[11–14] Irbesartan is strictly contraindicated in the second and third trimesters of pregnancy and during lactation.[15]

Drug interactions

Potential drug interactions with cytochrome P450 2C9 have been extensively analyzed.[16] Fluconazole, a cytochrome P450 2C9 inhibitor, increases steady-state peak plasma concentration (19%) and area under the curve (63%), without altering the time to peak plasma concentration.[17] No data are available regarding the impact of this interaction on antihypertensive efficacy. The pharmacokinetic profile of irbesartan is not affected by nifedipine, warfarin, simvastatin, tolbutamide, hydrochlorothiazide, or magnesium-aluminum hydroxide antacids. Irbesartan does not alter the steady-state pharmacokinetics of digoxin.[6,16] When combined with a cyclooxygenase 2 inhibitor in slightly volume-depleted subjects with normal renal function, irbesartan does not affect renal hemodynamics and renal salt handling.[18] A pharmacogenetic study has confirmed the role of the cytochrome P450 2C9 enzyme in the metabolism of irbesartan. In a Chinese population, carriers of the cytochrome P450 2C9*3 allele had higher levels of irbesartan at 6 and 14 hours.[19]

Therapeutic efficacy in hypertension

The antihypertensive efficacy of irbesartan has been established in numerous, large, randomized active-controlled or placebo-controlled trials of up to three months' duration.[20–34] As expected, irbesartan in monotherapy is superior to placebo in lowering both systolic and diastolic blood pressure.[15,30,31] The blood pressure effect was manifest within two weeks of starting treatment, and achieved maximum reduction after 2–6 weeks.[30] A dose-response relationship over a dose range of 1–900 mg once daily was observed, reaching a plateau with doses ≥300 mg once daily.[31] The placebo-subtracted reduction in office blood pressure was approximately 8–10/5–6 mmHg.[31] In studies involving ambulatory blood pressure assessment, irbesartan was effective in producing sustained 24-hour blood pressure control.[22,23,29,35] A trough-to-peak ratio ≥0.6 was achieved with doses ≥150 mg once daily.[31]

Comparative clinical trials performed in mild-to-moderate hypertension showed equal efficacy, but better tolerability, compared with the other major antihypertensive classes, ie, beta-blockers (atenolol), calcium antagonists (amlodipine), angiotensin-converting enzyme inhibitors (enalapril), and renin inhibitors (aliskiren), and superior efficacy as compared with doxazosin.[20–22,26–28,36–38] In intraclass comparative clinical trials (Table 2), irbesartan was at least as effective as losartan, significantly more effective than valsartan, but less effective than olmesartan at reducing office diastolic blood pressure.[24,25,35,39] However, in an additional analysis considering 24-hour ambulatory blood pressure values as a secondary variable, no significant difference was found between olmesartan and irbesartan in terms of blood pressure (13/9 mmHg for olmesartan 20 mg once daily versus 11/7 mmHg for irbesartan 150 mg once daily (not statistically significant), nor in terms of the percentage of patients reaching a mean 24-hour blood pressure <130/80 mmHg (21% versus 14%, not statistically significant).[40]

In a recent comparative study, we demonstrated significant differences between angiotensin receptor blockers in their capacity to induce sustained vascular blockade of angiotensin II receptors when the renin-angiotensin-aldosterone system is activated by a thiazide diuretic.[41] The blood pressure response to angiotensin II infusion was reduced by more than 90% with irbesartan 300 mg, irbesartan-hydrochlorothiazide 300/25 mg, and/or olmesartan-hydrochlorothiazide 20/25 mg, and by nearly 60% with valsartan-hydrochlorothiazide 160/25 mg and losartan-hydrochlorothiazide 100/25 mg (P < 0.05). In the kidney, angiotensin II infusion reduced renal plasma flow by 36% at baseline (P < 0.001). Irbesartan ± hydrochlorothiazide and olmesartan-hydrochlorothiazide blocked the renal hemodynamic response to angiotensin II almost completely, whereas valsartan-hydrochlorothiazide and losartan-hydrochlorothiazide only blunted this effect, by 34% and 45%, respectively.

Finally, a Portuguese group evaluated the effect of irbesartan on the circadian rhythm of blood pressure. In salt-sensitive

Table 2 Antihypertensive efficacy of irbesartan, comparing oral irbesartan monotherapy with other classes of antihypertensive drugs in patients with mild-to-moderate hypertension

Comparison class (agent)	Dosage (mg/day)	IRB noninferior	IRB superior	IRB inferior
ACE inhibitor				
ENA	IRB 150–300, ENA 10–20	Chiou et al[27]		
	IRB 150–300, ENA 10–20	Coca et al[22]		
	IRB 150–300, ENA 10–20	Lacourciere[20]		
	IRB 75–300, ENA 5–10	Mimran et al[21]		
Renin inhibitor				
ALI	IRB 150, ALI 150	Gradman et al[36]		
	IRB 150, ALI 300			Gradman et al[36]
Calcium channel blocker				
AML	IRB 150, AML 5	Gaudio et al[61]		
Beta-blocker				
ATE	IRB 75–150, ATE 50–100	Stumpe et al[28]		
Alpha-1 antagonist				
DOX	IRB 300, DOX 4		Derosa et al[38]	
Angiotensin II receptor blockers				
LOS	IRB 150, LOS 100		Kassler-Taub et al[24]	
	IRB 300, LOS 100	Kassler-Taub et al[24]		
	IRB 200, LOS 100	Yoshinaga[91]		
	IRB 150–300, LOS 50–100	Oparil et al[25]		
VAL	IRB 150, VAL 80		Mancia et al[23]	
OLM	IRB 150, OLM 20			Oparil et al[39]

Abbreviations: ACE, angiotensin-converting enzyme inhibitor; CCB, calcium channel blocker; BB, beta blocker; ATE, atenolol; IRB, irbesartan; ENA, enalapril; ALI, aliskiren; AML, amlodipine; LOS, losartan; OLM, olmesartan; VAL, valsartan; DOX, doxazosin.

hypertensive patients with a nondipper profile on a high-salt diet (n = 12), irbesartan restored the nocturnal blood pressure decline in a dose-dependent manner.[42]

Efficacy in hypertension when combined with other drugs

Combination of an angiotensin receptor blocker with hydrochlorothiazide provides additive blood pressure reduction. There is a strong pathophysiological rationale supporting this association. Diuretic-induced reduction in total body sodium provokes a secondary rise of renin, which may counterbalance its diuretic and antihypertensive effect. Simultaneously blocking the renin-angiotensin-aldosterone system prevents the action of a reactive hyperreninemia and maintains the blood pressure-lowering effect of salt depletion. The synergy between the two drugs has been shown in several clinical trials.

In a 4×4 placebo-controlled study involving 683 patients with mild-to-moderate hypertension, patients were randomized to one of 16 different double-blind combinations of irbesartan (0–300 mg once daily) and hydrochlorothiazide (0–25 mg once daily).[34] At week 8, mean changes from baseline in trough blood pressure and total responder rates increased in a dose-dependent manner in both the single therapy and combination therapy groups. Combination therapy was more effective than either drug alone.

Two placebo-controlled studies performed in patients with mild-to-moderate hypertension showed that irbesartan 75 mg or 150 mg + hydrochlorothiazide 12.5 mg reduced blood pressure more effectively than placebo or either drug alone in both seated trough blood pressure and 24-hour ambulatory blood pressure.[32,43] Irbesartan 150 mg + hydrochlorothiazide 12.5 mg once daily resulted in reductions of 4–7/2–4 mmHg, additional to those with the individual components.[15] Further, the combination therapy reduced blood pressure in patients inadequately controlled by monotherapy with irbesartan or hydrochlorothiazide.[33,44]

The largest trial demonstrating the efficacy of irbesartan-hydrochlorothiazide combination therapy was INCLUSIVE (Irbesartan-Hydrochlorothiazide Blood Pressure Reductions in Diverse Patient Populations), a prospective, open-label, single-arm study (n = 844). INCLUSIVE extended the previous reported findings by evaluating the efficacy and safety of a fixed combination in patients with uncontrolled systolic blood pressure after four weeks' monotherapy. Progressive uptitration to high-dose irbesartan-hydrochlorothiazide 300/25 mg once daily, if necessary, lead to substantial reductions in systolic blood pressure (-23.0 ± 13.3 mmHg, $P < 0.001$) between baseline and week 18, and allowed systolic blood pressure goals to be attained in 75% of patients.

Endothelial effects

Angiotensin II has emerged as a key mediator of arteriosclerosis, by various pathogenic pathways. It induces vasoconstriction, triggers oxidative stress, stimulates the release of

proinflammatory cytokines and growth factors, and induces a procoagulant state through activation of platelets and of the plasminogen-activator inhibitor. These pathophysiological effects are mediated by the AT1 receptor, whereas the AT2 receptor might have protective functions.[45] The vascular protective properties of irbesartan on vascular endothelium, proven in a number of in vitro and in vivo studies, have recently been reviewed in detail by Derosa.[46,47]

Efficacy in diabetic nephropathy

The efficacy of irbesartan at slowing the progression of renal damage in hypertensive type 2 diabetic patients was clearly demonstrated in PRIME (Program for Irbesartan Mortality and Morbidity Evaluation).[48] PRIME consisted of two large (n > 500), at least two years in duration, randomized, double-blind, placebo-controlled trials, ie, IRMA 2 (the Irbesartan Microalbuminuria Type 2 Diabetes on Hypertensive Patients trial)[49] and IDNT (the Irbesartan in Diabetic Nephropathy trial).[50]

The IRMA 2 trial was performed in patients (n = 590) with early-stage renal damage, as indicated by microalbuminuria (30–300 mg/day) but normal creatinine levels.[49] The aim of the study was to compare the effects of irbesartan 150 and 300 mg once daily and placebo on the progression to overt nephropathy, defined as the conversion of microalbuminuria to albuminuria. In the two years of follow-up, the primary endpoint of overt nephropathy was reached by significantly fewer recipients of irbesartan 300 mg once daily compared with placebo (unadjusted hazards ratio for diabetic nephropathy 0.3, 95% confidence interval [CI] 0.14–0.61, $P < 0.001$). Irbesartan 150 mg once daily significantly reduced urinary protein (albumin excretion rate) compared with placebo, but without attaining the primary endpoint. The effect of irbesartan on microalbuminuria was partly independent of its blood pressure-lowering effect.

IDNT evaluated the efficacy of irbesartan in 1715 hypertensive, type 2 diabetic patients with established nephropathy, as indicated by overt proteinuria (>900 mg/day) and elevated serum creatinine.[50] The relative risk of reaching the composite primary endpoint (doubling baseline serum creatinine level, onset of end-stage renal disease, or death from any cause) was significantly lower with irbesartan 300 mg once daily than with placebo (unadjusted relative risk 0.80, 95% CI 0.66–0.97; $P = 0.02$) or with amlodipine 10 mg once daily (unadjusted relative risk 0.77, 95% CI 0.63–0.93; $P = 0.006$). Again, the difference remained significant after adjustment for mean arterial pressure, suggesting a blood pressure-independent effect.

In a post hoc analysis of IDNT, the systolic blood pressure achieved strongly predicted renal outcome, and progressive lowering to 120 mmHg was associated with improved renal and patient survival, independently of baseline renal function.[51] Below this threshold, all-cause mortality increased. Additional evidence of a beneficial antiproteinuric effect of irbesartan beyond blood pressure control emerged from a small placebo-controlled crossover trial, where irbesartan improved microalbuminuria also in a normotensive subgroup of diabetic patients with early-stage microalbuminuric nephropathy.[52]

There are some arguments to explain this renoprotective effect. Irbesartan has been found to induce renal vasodilatation without altering glomerular filtration rate, to improve endothelial function, and to reduce oxidative stress and inflammation in the kidney.[49,53–58] In an animal model, irbesartan normalized the deficiency in podocytary nephrin expression, a protein involved in glomerular filtration barrier function.[59] All these data suggest that blockade of the AT1 receptor confers renal protection beyond its purely hemodynamic effect.

The recently published IMPROVE (Irbesartan in the Management of Proteinuric Patients at High Risk for Vascular Events) study analyzed the potential benefit of a dual blockade of the renin-angiotensin-aldosterone system on albuminuria, in a population of hypertensive, mainly diabetic (87% with type 2 diabetes, 2% with type 1 diabetes patients at high cardiovascular risk, with albuminuric kidney disease.[60] Patients were randomized to 20 weeks' treatment with ramipril 10 mg + irbesartan 150–300 mg (both once daily) or ramipril 10 mg + placebo. The study showed no further benefit on albuminuria reduction in patients treated with combination therapy, despite better blood pressure control. Subgroup analyses showed that the largest reduction in albuminuria occurred in patients with overt nephropathy, without reaching statistical significance.

Efficacy in cardiac disease

The evidence of a positive impact of irbesartan on left ventricular mass in patients with mild-to-moderate hypertension is based on two comparative trials, ie, an open-label/blinded-endpoint study (n = 60) and a randomized double-blind study (n = 115).[61,62] Over a six-month period, irbesartan 150–300 mg once daily was found to induce significantly greater left ventricular mass index regression than amlodipine 5–10 mg once daily and atenolol 50–100 mg once daily, despite similar blood pressure control.[61,62] Moreover, compared with atenolol, irbesartan significantly reduced QT

and corrected QT interval dispersion (the difference between maximal and minimal QT intervals within a 12-lead surface electrocardiogram), with a theoretical reduction in the risk of arrhythmias.[63] There was a similar improvement of diastolic function in both groups, related to changes in ventricular geometry and blood pressure control for irbesartan, and only to blood pressure reduction for atenolol.[64] Of note, similar beneficial cardiac effects have been demonstrated with other angiotensin receptor blockers, indicating that these effects are not unique to irbesartan.

In the IDNT trial, irbesartan reduced the incidence of congestive heart failure episodes (most, but not all, requiring hospitalization) compared with placebo (hazards ratio 0.72, 95% CI 0.52–1.0; $P = 0.048$) or amlodipine (hazards ratio 0.65, 96% CI 0.48–0.87; $P = 0.004$).[50,65]

More recently, the data of the I-PRESERVE trial have been published.[66] This was a large, multicenter, placebo-controlled trial performed in a population of 4128 patients ≥60 years, with New York Heart Association Class II–IV heart failure and an ejection fraction ≥45%. Despite a reduction in blood pressure of 3.6/1.9 mmHg over four years of follow-up, irbesartan 300 mg once daily did not yield cardiovascular benefits over placebo on the primary composite outcome of all-cause mortality or hospitalization for a cardiovascular cause. These data tend to confirm the absence of benefits of renin-angiotensin-aldosterone system inhibition in patients with diastolic dysfunction.

Data from studies with angiotensin-converting enzyme inhibitors provided evidence that the renin-angiotensin-aldosterone system is involved in atrial remodeling in atrial fibrillation. Some trials have evaluated the effect of irbesartan in atrial fibrillation. A Spanish prospective trial showed that adding irbesartan to amiodarone was more effective in the maintenance of sinus rhythm than amiodarone alone in patients with persistent atrial fibrillation after cardioversion to sinus rhythm.[67] Patients treated with amiodarone-irbesartan had a greater probability of remaining free of atrial fibrillation than patients treated with amiodarone alone over a median follow-up time of 254 days (79.5% versus 55.9%, $P = 0.007$).

This finding has recently been reconfirmed in a randomized, controlled Chinese trial performed in patients with atrial fibrillation following rheumatic valve replacement and cardioversion. The combination of amiodarone and irbesartan demonstrated a higher rate of maintenance of sinus rhythm (69.8% versus 40.5%, $P = 0.01$) and better atrial fibrillation-free survival ($P = 0.006$) than amiodarone alone during the one-year follow-up period.[68]

The ACTIVE-I study is part of a larger research program in atrial fibrillation, which 9016 patients enrolled in 41 countries were randomly assigned to receive irbesartan or placebo for a mean of 4.1 years.[69] The study was completed in June 2009. The difference in systolic blood pressure between the groups was approximately 3 mmHg. According to the study results, irbesartan was not associated with a reduction in the first coprimary endpoint of major vascular events, the composite of cardiovascular death, heart attack, or stroke (5.4% per year in each group, $P = 0.846$). There was a slight but nonsignificant reduction in the second coprimary endpoint of major vascular events plus hospitalization for heart failure (7.3% in the irbesartan group versus 7.7% in the placebo group, $P = 0.122$) due to a 14% reduction in the risk for heart failure hospitalization in the irbesartan group versus the placebo group (2.7% versus 3.2%, $P = 0.018$). A post hoc analysis revealed a 13% reduction in the composite endpoint of stroke, non-central nervous system embolism, and transient ischemic attack in patients taking irbesartan versus placebo (2.9% versus 3.4%, $P = 0.02$).

Safety and tolerability

Poor adherence with therapy has been recognized as a causal factor of failure of blood pressure control.[70] Persistence with a drug, defined as the time a patient remains on the prescribed medication, can be regarded as a good general indicator of the satisfaction of both patients and physicians with the efficacy and tolerability of the treatment. It is therefore not surprising that the persistence rate varies between drug classes. A British comparative study and a large Canadian cohort study showed angiotensin-converting enzyme inhibitors as the best and diuretics as the poorest persistence builders.[70,71] Data regarding persistence with angiotensin receptor blockers, not yet included in the previous studies, are now emerging. Two population-based trials including angiotensin receptor blockers revealed that patients have a better persistence with angiotensin receptor blockers than with all other antihypertensive drug classes up to three years.[72,73] In a European cohort study of 2416 newly diagnosed hypertensive patients treated with monotherapy by general practitioners, irbesartan scored highest, with a persistence rate at one year of 60.8%, compared with other angiotensin receptor blockers and other drug classes (Figure 1).[74] This improved persistence has been attributed in part to the efficacy of the compounds and mainly to the placebo-like side effect profile, verified for all clinically relevant dosages of irbesartan.[23,24,37,75,76] In a pooled analysis of nine 4–12-week, placebo-controlled studies involving 2606 mild-to-moderate hypertensive patients, the overall incidence of adverse events

was similar in the irbesartan group (<900 mg once daily) and placebo-treated group (21% versus 20%, respectively), without clinical relevant differences in type of adverse events.[75] Adverse events reported in ≥1% of irbesartan recipients and with a numerically higher incidence than with placebo, included diarrhea, dyspepsia/heartburn, and fatigue. None of these adverse events occurred at an incidence ≥5%. The tolerability profile of irbesartan is, in many aspects, comparable with that of other angiotensin receptor blockers.

The results of a post-marketing survey in Switzerland including 4769 hypertensive patients treated with irbesartan further emphasized the value of the good tolerability profile in enhancing treatment adherence.[77] Of the 4639 patients with complete follow-up data, 82.5% were persistent with irbesartan for more than four months. The tolerability profile emerged as the most important predictive factor of long-term persistence with therapy. The favorable safety profile was also confirmed in long-term treatment. In two-year extension studies, irbesartan as monotherapy or as combination therapy with hydrochlorothiazide was associated with low discontinuation rates for adverse events (5.3%–9.1%) and low incidences of serious adverse events (5.3%–8.6%).[78,79] In previously reported comparison studies with other antihypertensive major classes, the overall incidence of adverse events with irbesartan was similar to that of the comparator agent, including atenolol,[28] enalapril,[20–22,37] amlodipine,[26] doxazosin,[38] aliskiren,[36] and other angiotensin receptor blockers. The incidence of cough was significantly lower with irbesartan than with the angiotensin-converting enzyme inhibitor, enalapril (overall range 0%–10% versus 8%–21%, respectively).[20–22,27] However, the incidence of cough was comparable with other angiotensin receptor blockers.

The good tolerability profile is conserved when irbesartan is administered in combination with hydrochlorothiazide,
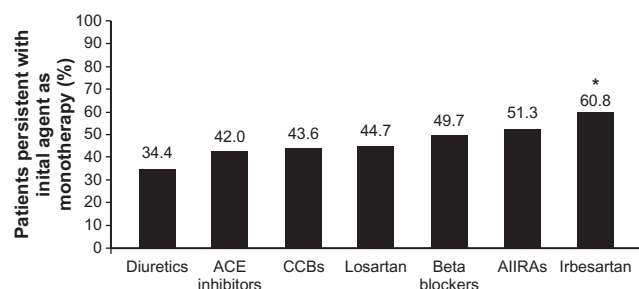
with an overall incidence rate of adverse events comparable with that of placebo. Adverse events, transient and mild, are similar to those found in irbesartan and/or hydrochlorothiazide monotherapy.[32–34] Safety and tolerability of fixed-dose irbesartan-hydrochlorothiazide for rapid control of severe hypertension has recently been confirmed in a randomized, controlled trial.[80] Despite more rapid and aggressive blood pressure-lowering, initial fixed-dose irbesartan-hydrochlorothiazide demonstrated a comparable adverse event profile to irbesartan monotherapy in patients with severe hypertension.

When considering hypertensive patients with type 2 diabetes and nephropathy, the adverse event experiences were generally similar to those reported by the hypertensive population. However, in the population with overt nephropathy in the IDNT trial, the incidence rates of dizziness, orthostatic dizziness, orthostatic hypotension, and hyperkalemia (≥6.0 mmol/L) were significantly higher with irbesartan 300 mg once daily than with placebo.[50] The occurrence of hyperkalemia led to significantly higher discontinuation rates in the irbesartan treated-group (1.9%) than in the placebo (0.5%) or amlodipine group (0.4%, $P = 0.01$ for both between-group comparisons). Of note, hyperkalemia is a relative contraindication to the prescription of blockers of the renin-angiotensin system, and the addition of an angiotensin receptor blocker, on top of an angiotensin-converting enzyme inhibitor or a direct renin inhibitor, may favor the development of life-threatening hyperkalemia, particularly in patients with reduced renal function.

Recent research has focused on the impact of irbesartan on quality of life and exercise performance in cardiology patients. In a randomized, controlled trial focused on cardiac insufficiency symptoms, irbesartan added to angiotensin-converting enzyme inhibitors produced significant improvement in physical capacity (six-minute hall-walk distance, $P < 0.01$), exercise time ($P = 0.01$), New York Heart Association class ($P < 0.005$), and quality of life score ($P < 0.005$) compared with placebo.[81]

Based on the results of IDNT, a number of modeled (Markov modeling) pharmacoeconomic analyses were published.[50] Treatment with irbesartan in hypertensive patients with type 2 diabetes and nephropathy resulted in improved life expectancy and appeared to be cost-saving compared with amlodipine or control therapy over a prospective period of 10 years and/or 25 years for the US, Canada, and some European countries (Belgium, France, Italy, Spain, UK).[82–87] The early initiation of irbesartan (at the microalbuminuric stage) improved life expectancy and saved costs compared with later initiation (in the presence of overt nephropathy).[88]

Figure 1 Persistence at one year by antihypertensives.[74]
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Notes: *$P = 0.001$ versus all other antihypertensive classes and versus losartan; $P = 0.009$ versus all other angiotensin II receptor antagonists.
Abbreviations: ACE, angiotensin-converting enzyme; CCBs, calcium channel blockers; AIIRAs, angiotensin II receptor antagonists.

Conclusion

Used as monotherapy or in association with hydrochlorothiazide, irbesartan is an effective antihypertensive drug in a variety of mild-to-moderate hypertensive populations, including patients with diabetes, obesity, renal insufficiency, and cardiovascular disease. In comparative trials, irbesartan is at least as effective and sometimes superior to comparator agents of the major antihypertensive classes. There is some evidence that irbesartan provides protective cardiovascular effects beyond its antihypertensive action. This is particularly true for its beneficial effects on slowing the progression of early-stage and late-stage renal disease in hypertensive patients with type 2 diabetes and on promoting regression of left ventricular mass in patients with hypertension and left ventricular hypertrophy. Recent research has further highlighted the positive role of irbesartan in preventing recurrence of arrhythmia in patients with persistent atrial fibrillation, when added to classical antiarrhythmic therapy. Finally, some data suggest an additional benefit in cardiac disease, through a reduction in the risk of heart failure episodes, as observed with other angiotensin receptor blockers.

In addition to its therapeutic efficacy, irbesartan can claim, like other angiotensin receptor blockers, an extremely favorable, placebo-like side effect profile, as has been shown in numerous real-life trials, even in the long term. It is therefore not surprising that irbesartan scores well for patient acceptation and adherence rates.

Disclosure

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