Clinical Overview of Irbesartan
A New Angiotensin II Receptor Antagonist

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Irbesartan is an angiotensin II receptor (AT₁ subtype) antagonist that has been extensively studied in the Bristol-Myers Squibb/SanoI clinical development program. As shown in seven placebo controlled clinical trials, irbesartan provides clinically significant dose related reductions in blood pressure in patients with mild-to-moderate hypertension. Once daily dosing provides full 24 h blood pressure control with blood pressure reductions equivalent to those of twice daily dosing, and long-term control with monotherapy in a high percentage of patients. The antihypertensive effect of irbesartan is comparable to or exceeds that of leading antihypertensive agents. Whereas irbesartan demonstrates a relationship between dose and antihypertensive effect, there is no such relationship between dose and rates of adverse events or discontinuations due to adverse events, the incidence of which are comparable to those with placebo. Thus, irbesartan provides significant dose related antihypertensive effects with placebo-like tolerability. Am J Hypertens 1997; 10:318S–324S © 1997 American Journal of Hypertension, Ltd.

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Irbesartan is a potent, noncompetitive, long acting angiotensin II receptor antagonist (AIIRA) that is specific for the AT₁ receptor subtype.1–3 Also known as SR 47436 and BMS-186295, irbesartan was discovered by Sanofi Recherche (Paris, France) and is under joint clinical development by Sanofi Pharmaceuticals and Bristol-Myers Squibb (Princeton, NJ). Clinical experience with irbesartan in hypertension is extensive, with more than 8500 persons treated in clinical trials, approximately 2000 of whom have been treated for ≥1 year.

IRBESARTAN CLINICAL EFFICACY

Results of Placebo Controlled Trials The results of randomized, placebo controlled trials demonstrate clinically significant reductions in blood pressure, a clear relationship between dose and antihypertensive response, and full 24 h blood pressure control with once daily irbesartan.

To examine the relationship between irbesartan dose and blood pressure lowering, a double blind, placebo controlled phase II study was conducted in 319 patients with mild-to-moderate hypertension (mean blood pressure, 150/101 mm Hg) (data on file, Bristol-Myers Squibb/SanoI). Patients were randomized to treatment with placebo or irbesartan doses of 100, 200, or 300 mg once daily for 8 weeks. Irbesartan demonstrated a dose-related reduction in trough seated diastolic blood pressure (SeDBP) and systolic blood pressure (SeSBP). Significant blood pressure lowering was evident as early as 2 weeks after the start of therapy, and further reductions were achieved over the next 6 weeks. The percentage of total responders (SeDBP < 90 mm Hg or reduced by ≥ 10 mm Hg from baseline) after 8 weeks was approximately 70% with the irbesartan 300 mg dose.

An ambulatory blood pressure monitoring study was performed to compare the effects of irbesartan...
once daily dosing with twice daily dosing on blood pressure lowering, and also to assess the effect of irbesartan over 24 h.4 Patients with mild-to-moderate hypertension (n = 215; mean blood pressure, 158/101 mm Hg and 24 h ambulatory diastolic blood pressure > 85 mm Hg) were randomized to placebo or irbesartan 75 or 150 mg once daily or 75 mg twice daily. All irbesartan regimens significantly reduced mean 24 h ambulatory diastolic and systolic blood pressure. Similar reductions in ambulatory blood pressure over 24 h were seen with 150 mg once daily and 75 mg twice daily (Figure 1). At trough (24th h), there appeared to be a slight benefit with the once daily regimen. These results indicate that once daily and twice daily dosing produced equivalent reductions in blood pressure, and there was no need for twice daily dosing with irbesartan.

An integrated analysis of efficacy was performed by combining the results of all seven placebo controlled trials conducted with irbesartan in patients with mild-to-moderate hypertension (data on file, Bristol-Myers Squibb/Sanofi). Data were integrated across all studies by analysis of covariance (ANCOVA) methods in order to characterize the irbesartan dose–response relationship. A total of 2230 patients who had been treated with irbesartan doses of 1 mg to 900 mg for a period of 6 to 8 weeks were included in this analysis. The 150 mg dose provided an average reduction in SeSBP/SeDBP of 211.6/29.4 mm Hg versus 23.3/24.2 mm Hg for placebo. Statistically and clinically significant decreases in SeDBP and SeSBP were seen with once daily doses of irbesartan 150 mg to 900 mg, with a plateau in effect at doses > 300 mg daily.

A similar integrated analysis was performed to assess the proportion responding (SeDBP <90 mm Hg or reduced ≥10 mm Hg from baseline) over the same dose range of 1 to 900 mg. Responder rates were 25% for placebo, 45% for irbesartan 75 mg, 55% for irbesartan 150 mg, and 60% for irbesartan 300 mg. The percentage of patients demonstrating a therapeutic response plateaued at irbesartan doses of 300 mg or greater. These results show a clear relationship between irbesartan dose and control of hypertension.

Trough:peak (T:P) ratio was also examined across these same placebo controlled studies. A placebo adjusted T:P ratio for SeDBP was computed for each irbesartan group according to the formula: [(adjusted mean change in trough SeDBP for irbesartan group) – (adjusted mean change in trough SeDBP for placebo group)] ÷ [(adjusted mean change in peak SeDBP for irbesartan group) – (adjusted mean change in peak SeDBP for placebo group)].

This analysis showed that the T:P ratio for once daily irbesartan was approximately 70% across the therapeutic range.

The long-term efficacy of irbesartan was assessed in an open label extension study in 171 patients with mild-to-moderate hypertension in which patients were treated with irbesartan monotherapy at doses up to 300 mg, followed by the addition of atenolol or hydrochlorothiazide (data on file, Bristol-Myers Squibb/Sanofi). Diastolic blood pressure continued to decline over a 12-month period. At the end of 12 months, 69% of patients achieved normalized blood pressure (SeDBP <90 mm Hg) with irbesartan monotherapy. An additional 22% of patients were effectively controlled with combination therapy at 12 months, for a total of 91% normalization on an irbesartan based regimen (Figure 2).

Results of Comparative Trials Several double blind, randomized, controlled trials compared the antihypertensive effects of irbesartan versus leading antihypertensive agents. These included two comparative trials with the angiotensin converting enzyme (ACE) inhibitor enalapril; one trial with the β-blocker atenolol; one with the calcium channel blocker amlodipine, and two with the diuretic hydrochlorothiazide.

The antihypertensive effects of irbesartan and enalapril were compared in a 12-week, double blind
study in patients with mild-to-moderate hypertension (SeDBP 95 to 110 mm Hg).\(^5\) Patients randomized to irbesartan (\(n = 98\)) initially received 75 mg once daily, which could be titrated to 150 mg once daily after 4 weeks and to 300 mg once daily after 8 weeks if SeDBP remained \(\geq 90\) mm Hg. Patients randomized to enalapril (\(n = 102\)) initially received 10 mg once daily, which could be titrated to 20 mg after 4 weeks and to 40 mg after 8 weeks if SeDBP remained \(\geq 90\) mm Hg.

Reductions in blood pressure were similar with the irbesartan and enalapril regimens throughout the 12-week study. The percentage of patients whose blood pressure was normalized (SeDBP <90 mm Hg) was also similar for each regimen at all time points (Figure 3). Thus, treatment with irbesartan provided at least equivalent efficacy to full doses of enalapril (ie, up to 40 mg daily) in patients with mild-to-moderate hypertension.

A comparative study with irbesartan and enalapril was also conducted in patients with severe hypertension (SeDBP 115 to 130 mm Hg).\(^6\) In this 12-week, double blind study, patients randomized to irbesartan (\(n = 121\)) initially received 150 mg once daily, which could be titrated to 300 mg after 1 week if SeDBP remained \(\geq 106\) mm Hg or after 2 weeks if SeDBP remained \(\geq 90\) mm Hg. Those randomized to enalapril (\(n = 61\)) initially received 20 mg once daily, which could be titrated to 40 mg once daily if the same blood pressure criteria were met. If SeDBP remained \(\geq 90\) mm Hg, open label antihypertensive therapies (hydrochlorothiazide, sustained release nifedipine, or oral atenolol) could then be added to the double blind study medication.

The irbesartan and enalapril regimens produced similar reductions in blood pressure at each time point (Figure 4). This was true even at weeks 1 and 2, when essentially all patients were still on monotherapy. The

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N = 95 patients/group
* Titrated at 4-week intervals for SeDBP \(\leq 90\) mm Hg
** SeDBP < 90 mm Hg

FIGURE 2. Long-term efficacy of irbesartan monotherapy and combination therapy.

FIGURE 3. Antihypertensive effects of irbesartan versus the ACE inhibitor enalapril in patients with mild-to-moderate hypertension.
proportion of patients normalized with the irbesartan regimen was slightly greater than with the enalapril regimen through the first 8 weeks of the study. By 12 weeks, the normalization rates were similar. During the early weeks of the study, more patients in the enalapril group did not achieve target blood pressure (SeDBP >90 mm Hg), and they required additional antihypertensive medications compared with the irbesartan group. In summary, as in patients with mild-to-moderate hypertension, an irbesartan regimen provided at least equivalent efficacy to a full dose enalapril regimen in patients with severe hypertension.

Irbesartan was compared with atenolol in patients with mild-to-moderate hypertension. Patients were randomized to double blind treatment with irbesartan 75 mg once daily (n = 110), which could be titrated to 150 mg after 6 weeks for SeDBP >90 mm Hg, or with atenolol 50 mg once daily (n = 121), which could be titrated to 100 mg at the same time point. At 12 weeks, open label hydrochlorothiazide followed by sustained release nifedipine were added to the double blind regimen if patients had not achieved target blood pressure (SeDBP <90 mm Hg). Both irbesartan and atenolol based regimens produced similar reductions in blood pressure at 24 weeks. At week 12, before additional antihypertensive agents were administered, more patients treated with irbesartan (72%) achieved a therapeutic response (SeDBP >90 mm Hg or reduced <10 mm Hg from baseline) than with atenolol (63%) (Figure 5). Thus, irbesartan provided at least comparable efficacy to full doses of atenolol (ie, up to 100 mg) in patients with mild-to-moderate hypertension.

Irbesartan was compared with amlodipine in hypertensive patients with type 2 diabetes and proteinuria.8
Patients were randomized to double blind treatment with irbesartan 75 mg once daily ($n=24$) or amlodipine 2.5 mg once daily ($n=23$). Doses of study medication could be doubled at weeks 4 and 8 if peak SeDBP $>70$ mm Hg or peak SeDBP $>110$ mm Hg.

Reductions in SeDBP were similar in both groups at all time points (2 to 6 mm Hg). Whereas there were no changes from baseline in serum creatinine in either group, treatment with amlodipine resulted in a significant decrease from baseline in creatinine clearance (23 mL/min/1.73m$^2$; $P<.01$) compared with that seen with irbesartan.

Two studies compared the antihypertensive effects of irbesartan and hydrochlorothiazide. In a double blind, placebo controlled study, the combination of irbesartan and hydrochlorothiazide was compared with the individual components in 819 patients with mild-to-moderate hypertension (data on file, Bristol-Myers Squibb/Sanofi). Mean trough and peak SeDBP and SeSBP at week 12 were significantly reduced in all active treatment groups when compared with placebo. Mean changes from baseline in trough SeSBP/SeSBP at week 12 were $-3.3/-5.1$, $-9.1/-8.2$, $-8.5/-8.5$, and $-11.9/-9.7$ for placebo, hydrochlorothiazide 12.5 mg, irbesartan 75 mg, and irbesartan 150 mg, respectively.

In a placebo controlled $4 \times 4$ matrix study conducted in 683 patients, irbesartan doses were 0, 37.5, 100, and 300 mg, and hydrochlorothiazide doses were 0, 6.25, 12.5, and 25 mg. As expected, a dose-response relationship was evident with irbesartan alone and with hydrochlorothiazide alone, and there was a clear benefit when the two agents were combined.

**ADDITIVE EFFECTS OF IRBESARTAN AND HYDROCHLOROTHIAZIDE**

The combination of irbesartan and hydrochlorothiazide provides added antihypertensive effects. In an extension of the phase II randomized, double blind, placebo controlled trial conducted in 319 patients with mild-to-moderate hypertension as previously discussed, hydrochlorothiazide 12.5 mg daily was added at week 9 if SeDBP was $\geq 90$ mm Hg and was contin-
ued for 2 weeks (data on file, Bristol-Myers Squibb/Sanofi). Whereas all three doses of irbesartan (100, 200, and 300 mg) produced statistically significant reductions in trough SeDBP at weeks 2, 4, 6, and 8 when compared with placebo, the addition of hydrochlorothiazide resulted in further reductions in SeDBP ranging from 1.6 mm Hg in the placebo group (n = 42) to 7.7 mm Hg in the irbesartan 300 mg group (n = 21). In the matrix study described above there was a clear additive benefit when the hydrochlorothiazide and irbesartan were combined, with reductions in diastolic blood pressure of up to 15 mm Hg and reductions in systolic blood pressure of up to 23 mm Hg.

IRBESARTAN SAFETY AND TOLERABILITY

Irbesartan demonstrated a placebo-like tolerability profile, even at the highest doses administered. An integrated analysis combined all safety data from nine placebo controlled, 4 to 12 week irbesartan monotherapy studies (irbesartan, n = 1965; placebo, n = 641). In this analysis, the adverse events profile with irbesartan was similar to that of placebo (Figure 6) (data on file, Bristol-Myers Squibb/Sanofi). The most commonly reported adverse events for irbesartan and placebo, respectively, were headache (12.3% versus 16.7%; P = .005), upper respiratory tract infection (8.5% versus 6.2%), musculoskeletal pain (6.6% versus 6.6%), and dizziness (4.9% versus 5.0%).

Adverse event rates and discontinuation rates were also assessed by irbesartan dose (Figure 7). There was no relationship between irbesartan dose and the incidence of adverse events or discontinuation rates due to adverse events. Furthermore, adverse event and discontinuation rates with irbesar-
Irbesartan were similar to or lower than those with placebo at all clinical doses.

There was also no difference in the incidence of cough between irbesartan and placebo in placebo controlled trials (2.8% and 2.7%, respectively) (Figure 8). In active controlled trials in which the presence of cough was specifically elicited from patients, the incidence of cough with irbesartan (4.5%) was slightly higher than that seen with irbesartan in placebo controlled trials; however, it was significantly lower than with the ACE inhibitor enalapril (15.3%), and similar to that for other non-ACE inhibitor antihypertensive agents.

There were no significant effects of irbesartan on hematologic indices or serum chemistry, including sodium, potassium, BUN, creatinine, uric acid, and total cholesterol.

SUMMARY
Irbesartan provides clinically significant reductions in blood pressure, with substantial reductions evident within 2 weeks of initiation of therapy. There is a clear relationship between irbesartan dose and antihypertensive response (Figure 9) and all irbesartan doses provide placebo-like tolerability. Once daily dosing provides consistent blood pressure lowering throughout the full 24 h period. Irbesartan achieves excellent long-term control of blood pressure with monotherapy. The efficacy of irbesartan is comparable to or exceeds that of full doses of leading antihypertensive drugs.

REFERENCES