

Hypertension

JOURNAL OF THE AMERICAN HEART ASSOCIATION



Learn and Live SM

Dose-Related Efficacy of Irbesartan for Hypertension : An Integrated Analysis

Richard A. Reeves, Chen-Sheng Lin, Kenneth Kassler-Taub and Hubert Pouleur

Hypertension 1998;31;1311-1316

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 72514

Copyright © 1998 American Heart Association. All rights reserved. Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://hyper.ahajournals.org/cgi/content/full/31/6/1311>

Subscriptions: Information about subscribing to Hypertension is online at
<http://hyper.ahajournals.org/subscriptions/>

Permissions: Permissions & Rights Desk, Lippincott Williams & Wilkins, a division of Wolters Kluwer Health, 351 West Camden Street, Baltimore, MD 21202-2436. Phone: 410-528-4050. Fax: 410-528-8550. E-mail:
journalpermissions@lww.com

Reprints: Information about reprints can be found online at
<http://www.lww.com/reprints>

Dose-Related Efficacy of Irbesartan for Hypertension

An Integrated Analysis

Richard A. Reeves, Chen-Sheng Lin, Kenneth Kassler-Taub, Hubert Pouleur

Abstract—Results of eight multicenter, randomized, placebo-controlled, double-blind, parallel-group studies were pooled to assess the efficacy of the angiotensin II–receptor blocker irbesartan over the dose range of 1 to 900 mg. A total of 2955 adults with a seated diastolic blood pressure of 95 to 110 mm Hg were randomized to treatment with oral irbesartan once daily or placebo for 6 to 8 weeks. Office blood pressure was measured at trough (24 ± 3 hours after the last dose) and peak (3 ± 1 hours after the last dose) by mercury sphygmomanometry. Demographic characteristics (mean blood pressure; 151/101 mm Hg; mean age, 54 years; 63% male; and 82% white) were similar across all dose groups. After the groups were pooled, antihypertensive efficacy was assessed by therapeutic response (trough seated diastolic blood pressure < 90 mm Hg or a reduction from baseline of ≥ 10 mm Hg) and by modeling of the maximum reductions in trough and peak seated diastolic and systolic blood pressure. Antihypertensive effects increased with increasing doses and reached a plateau at ≥ 300 mg. Irbesartan 150 mg provided placebo-subtracted reductions in trough seated systolic and diastolic blood pressure of ≈ 8 and ≈ 5 mm Hg, respectively, with 56% of patients displaying a favorable response. In conclusion, irbesartan provides clinically significant blood pressure lowering, with a clear relationship between (log) dose and antihypertensive effect. (*Hypertension*. 1998;31:1311-1316.)

Key Words: irbesartan ■ dose response ■ randomized controlled trials ■ placebo

Irbesartan, developed jointly by Bristol-Myers Squibb and Sanofi, is a potent, long-acting, orally active Ang II receptor blocker with high selectivity for the angiotensin 1 receptor subtype.¹⁻³ The Ang II receptor blockers are a new class of antihypertensive agents that inhibit the renin-angiotensin system by blocking the Ang II receptor.⁴ In normotensive subjects, irbesartan resulted in dose-dependent increases in plasma renin activity and plasma Ang II levels.⁵ At doses of 150 and 300 mg, the pharmacological effects of irbesartan were long acting, with increases in plasma renin activity and Ang II still present at 24 hours.

This article analyzes the integrated dose-response results from eight large, multicenter, randomized, double-blind, placebo-controlled studies of patients with mild to moderate hypertension (for a list of studies, see Table 1). The benefits of analyzing pooled data¹⁰ include increased statistical power over individual trials and more precise estimation of patient benefit from therapy.¹¹ The homogeneity of study design, conduct, and patient population among these eight irbesartan studies allowed for a meaningful integrated analysis.

Fully defined dose-response relationships are rarely established during clinical drug development.¹² Unfortunately, failure to properly define the lower end of the dose-response relationship and hence, the lowest effective dose, has been responsible for the introduction of many antihypertensive drugs into clinical practice at excessively high doses. Because

efficacy data are often incomplete due to failure to adequately explore the lower or upper extreme of the dose, E_{\max} analysis of receptor-blocking drugs has only occasionally been used in phase II and phase III clinical trials. With irbesartan, E_{\max} analysis was possible because of the absence of dose-limiting side effects even at the maximum doses.¹³ Knowledge of the full dose response is clinically useful because it provides a rational basis for titration based on expected effect.

The primary objectives of this integrated analysis were to assess (1) the relationship between irbesartan dose and efficacy as assessed by the mean change (from baseline) in trough and peak SeDBP and SeSBP measurements versus placebo and (2) the relationship between irbesartan dose and the percentage of patients showing a favorable response to the drug (trough SeDBP < 90 mm Hg or a reduction from baseline of ≥ 10 mm Hg).

Methods

Patient Selection

Men and surgically sterile or postmenopausal women were 18 years of age or older and all had newly discovered or established mild to moderate essential hypertension (office SeDBP, 95 to 110 mm Hg). In one study, which included both office blood pressure assessments and ambulatory blood pressure monitoring, patients were also required to have a baseline mean ambulatory DBP ≥ 85 mm Hg.

Exclusion criteria pertained to specific concomitant diseases that would present safety hazards or to concomitant medications that

Received October 24, 1997; first decision November 18, 1997; revision accepted February 10, 1998.

From Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ.

Reprint requests to Richard A. Reeves, MD, Bristol-Myers Squibb Pharmaceutical Research Institute, Rte 206 at Provinceline Rd, PO Box 4000, Princeton, NJ 08543-4000.

E-mail richard_a_reeves@ccmail.bms.com

© 1998 American Heart Association, Inc.

Selected Abbreviations and Acronyms

Ang II = angiotensin II
D ₅₀ = dose at which 50% of the maximum blood pressure reduction was observed
E _{max} = maximum blood pressure reduction
DBP = diastolic blood pressure
SBP = systolic blood pressure
Se = seated
T:P = trough to peak

might interfere with the assessment of safety or efficacy of irbesartan (eg, drugs that can potentially affect blood pressure), and these criteria were highly uniform across studies. Each study was approved by an institutional review committee, and each patient gave informed consent before study enrollment.

Study Design

All studies consisted of a 4- to 5-week, single-blind, placebo lead-in phase for qualification followed by a 6- to 12-week double-blind, parallel-group, fixed-dose phase in which patients were randomized to receive either oral irbesartan or placebo once daily in the morning. All previous antihypertensive agents were withdrawn after consent was obtained and before the lead-in phase. During double-blind therapy, patients generally returned for clinic visits at 2-week intervals. Per protocol, patients were to be withdrawn from a study for lack of efficacy, ie, an SeSBP >200 mm Hg or an SeDBP >112 mm Hg, confirmed within ≤3 days. In addition, some patients were withdrawn by the investigator for blood pressure measurements, which although below these limits, were considered to be too high or inadequately controlled.

Observation Methods

In all studies, blood pressure was measured with a standard, calibrated, mercury sphygmomanometer. (In the ambulatory blood pressure study,⁸ only the trough office blood pressures were used in the integrated analysis.) Trough measurements were performed 24±3 hours after the previous day's morning dose. Peak effects were assessed 3 to 4 hours after dosing. After 5 to 10 minutes of rest in the seated position, blood pressure was determined by calculating the mean of three to five replicate measurements taken 1 minute apart. Heart rate was measured by counting the pulse for 30 seconds and multiplying by 2.

Outcome Measures

In each study, the primary outcome measure as dictated by the protocol was the change (from baseline) in trough SeDBP after 6 to 12 weeks of therapy; therefore, this measure was used for the integrated analysis. Also measured at the same time were the change from baseline in trough SeSBP and the percentage of patients who

TABLE 1. Studies Included in Pooled Analysis

Study	Number of Sites Participating in Study	Location
002 ⁶	45	US, Canada
025 ⁶	35	US
029 ⁷	27	US, Canada
030 ⁸	16	Italy
037 ¹⁷	46	US
038 ¹⁸	63	US, Latin America
050	54	US
066 ⁹	41	US, Canada, Latin America

TABLE 2. Results for E_{max} and Sigmoidal E_{max} Models*

Variable	Hill Coefficient	Residual Mean		
		Squared Error†	E _{max} , mm Hg	D ₅₀ , mg
Trough SeDBP	1	53.96	7.13	64.9
	1.26	51.97	6.63	58.8
Trough SeSBP	1	173.72	12.57	86.1
	1.38	173.69	11.30	73.7
Peak SeDBP	1	74.24	9.20	52.7
	0.92	74.29	9.44	55.0
Peak SeSBP	1	193.59	12.85	41.9
	1.06	193.72	12.65	41.2

*For each variable, results are given on the first line for the E_{max} model (Hill coefficient = 1) and on the second line for the more general sigmoidal E_{max} model, wherein the coefficient is estimated as shown.

†Residual mean squared error was larger in the model with the Hill coefficient due to one degree of freedom fewer in the error term.

achieved a satisfactory therapeutic response (defined as a trough SeDBP <90 mm Hg or an SeDBP reduced by ≥10 mm Hg from baseline). Peak SeDBP and SeSBP effects were determined from group mean hourly blood pressure values (in one protocol) or were measured at the approximate time of irbesartan's peak antihypertensive effects, 3±1 hours after dosing (in five protocols). On the day of peak value assessment, patients were given their day's dose in the office by study personnel.

Statistical Methods

Data from common irbesartan doses and placebo across all studies were pooled at times common to the studies and when maximal effects had usually been achieved (ie, after 6 to 8 weeks of treatment with a stable dose of irbesartan or placebo). The integrated analyses included all data from all randomized patients who had both a baseline assessment (last assessment before the double-blind medication) and an assessment at week 8 (week 6 in one protocol). The integrated analyses of peak blood pressure changes were based on the subset of randomized patients who had valid baseline assessments and valid peak assessments at week 8 (or week 6). To be considered valid, the assessments had to satisfy relevant protocol eligibility and compliance criteria (eg, peak blood pressure assessments were excluded if the timing relative to drug administration seriously deviated from the protocol specification). Validity for each subject was determined by the study monitor before the study unblinding.

Placebo-subtracted reductions from baseline in SeDBP and SeSBP over the entire dose range (1 to 900 mg) were fitted to E_{max} models. The E_{max} model was chosen because it describes the well-known sigmoidal log(dose)-response relationship expected with a receptor-antagonist drug,¹⁴ and as will be shown, the entire therapeutic range of irbesartan was examined.

The data were initially fit to the more general sigmoidal E_{max} model, which includes a parameter (the Hill coefficient) for "steepness" of the curve. Because inclusion of this parameter did not appreciably enhance the fit of the curve (see Table 2), this coefficient was set equal to 1, and the following simpler E_{max} model was used:

$$E_{ij} - P_i = (E_{\max} \cdot D_{ij}) \div (D_{50} + D_{ij})$$

where E_{ij} is the blood pressure reduction from baseline for subject j in study i ; P_i is the mean blood pressure reduction from baseline in subjects randomized to receive placebo in study i ; and D_{ij} is the dose of irbesartan for subject j in study i . Least-squares estimates of E_{max} and D₅₀ were generated from the above model by the Gauss-Newton iterative method to regress the residuals onto the partial derivatives of the model with respect to the parameters; initial values of 7 mm Hg and 60 mg for E_{max} and D₅₀, respectively, were used.

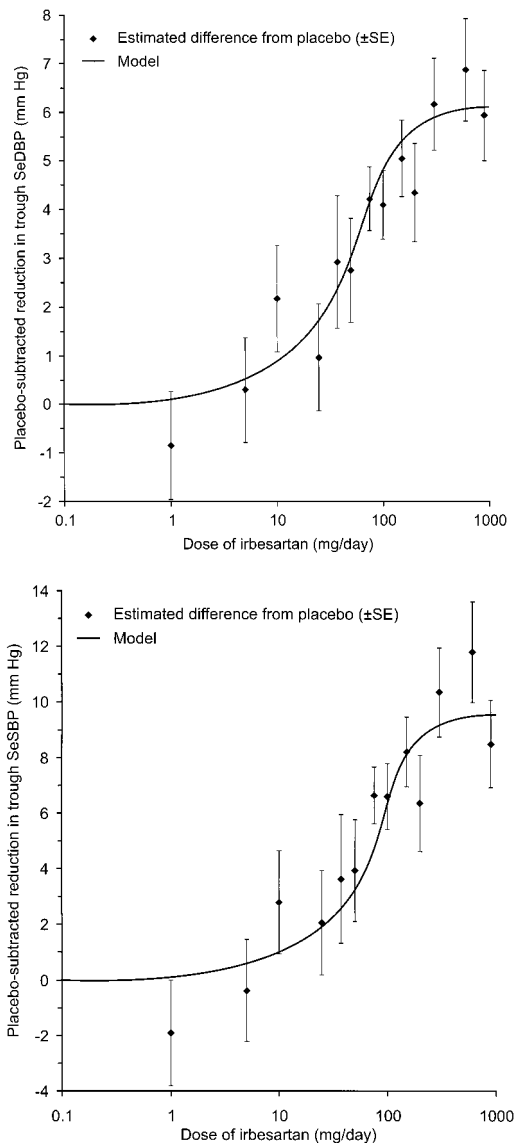


Figure 1. Placebo-subtracted reductions in mean trough SeDBP (top) and SeSBP (bottom) by irbesartan dose: E_{\max} model.

The prespecified analyses were, by nature, somewhat conservative, because given irbesartan's established antihypertensive effects, subjects were more likely to be withdrawn early from the study for insufficient blood pressure control from the placebo and low-dose groups than from the groups that received therapeutic doses of the active drug. Therefore, as a check on the primary analysis, a last-observation-carried-forward (LOCF) analysis was performed post hoc. This analysis was based on the last available trough blood pressure measurement after randomization. Because only a small fraction of patients did not have final visit (week 8 or week 6) data available, the LOCF result was expected to differ only slightly from the planned analysis.

The T:P ratio for SeDBP, adjusted for placebo effects, was calculated for each active-dose group according to the formula: $T:P = [(\text{adjusted mean change in trough SeDBP for the active group}) - (\text{adjusted mean change in trough SeDBP for the placebo group})] \div [(\text{adjusted mean change in peak SeDBP for the active group}) - (\text{adjusted mean change in peak SeDBP for the placebo group})]$.

Only SeDBP measurements from subjects who satisfied the eligibility criteria for efficacy and compliance were used for the T:P analysis. In addition, for analysis of the T:P ratio, subjects had to

have valid SeDBP measurements at baseline (ie, during the single-blind, placebo lead-in therapy) and valid peak and trough SeDBP assessments at the time analyzed (6, 8, or 12 weeks, depending on the protocol). It should be noted that the trough assessment assumes that each patient took his or her assigned dose on the day prior to the measurement; ie, patients were not observed to have ingested that dose. The proportion of responders (SeDBP <90 mm Hg or a reduction from baseline of ≥ 10 mm Hg) was tabulated for each dose as well as for the placebo group.

Results

Allocation of Patients to Study Groups

A total of 2955 patients were randomized into the irbesartan ($n=2197$) or placebo ($n=758$) arms of the eight studies. Only 2% of irbesartan-treated patients versus 5% of placebo-treated patients were withdrawn from the study owing to a lack of efficacy; 3% of irbesartan-treated and 4% of placebo-treated patients were discontinued because of an adverse event. A total of 2631 patients (1954 irbesartan and 677 placebo) had both baseline and end-point assessments and were therefore included in the primary analysis. The numbers of patients in the irbesartan dose groups were as follows: 1 mg, 68; 5 mg, 74; 10 mg, 72; 25 mg, 70; 37.5 mg, 40; 50 mg, 77; 75 mg, 277; 100 mg, 188; 150 mg, 486; 200 mg, 75; 300 mg, 350; 600 mg, 92; and 900 mg, 85. Of the 2197 patients randomized into the irbesartan arms, 2079 had at least one postrandomization value for trough seated blood pressure and were therefore included in the LOCF analysis.

Patient Demographics

Demographic characteristics and baseline blood pressures were similar across the integrated irbesartan dose groups and the placebo group. Subjects were generally in their early to middle fifties (mean age, 54 years), 82% were white, and 63% were male. The baseline mean seated blood pressure for all randomized patients was 151/101 mm Hg. In addition, because of the generally uniform inclusion and exclusion criteria across individual studies, these characteristics were similar between dose groups within and between each study (data not shown).

Reduction in Blood Pressure at Trough

In each individual study, the reduction from baseline in office trough SeDBP with irbesartan doses of ≥ 75 mg once daily was statistically significantly greater than with placebo (each $P < 0.01$). Trough SeSBP results were similar. Trough blood pressure reductions for a given dose were generally consistent across trials.

The results from the E_{\max} model for trough blood pressure are shown in Figure 1 and Table 2. The predicted E_{\max} values were 7.1 mm Hg for trough SeDBP and 12.6 mm Hg for trough SeSBP (reduction over placebo). From this integrated model, it can be inferred that an irbesartan dose of 150 mg once daily should produce a trough SeDBP reduction of ≈ 5 mm Hg over placebo and a trough SeSBP reduction of ≈ 8 mm Hg over placebo. An irbesartan dose of 300 mg once daily should produce corresponding placebo-subtracted reductions of ≈ 6 and ≈ 10 mm Hg, respectively. Only modest additional benefit would be expected with irbesartan doses beyond 300 to 600 mg.

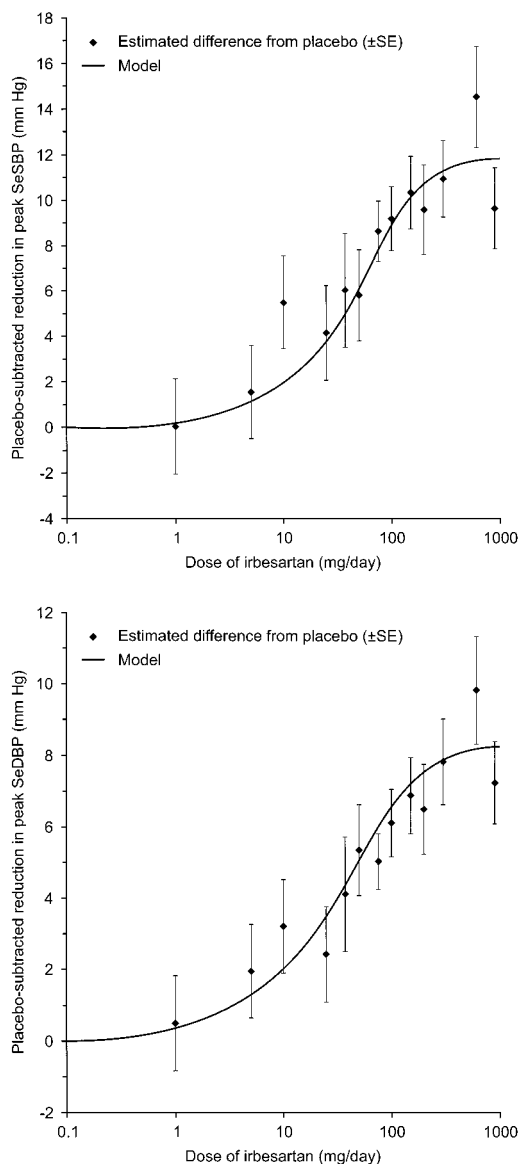


Figure 2. Placebo-subtracted reductions in mean peak SeDBP (top) and SeSBP (bottom) by irbesartan dose: E_{\max} model.

Reductions in Blood Pressure at Peak

The results from the E_{\max} model for peak blood pressure reductions are shown in Figure 2 and Table 2. The predicted E_{\max} values are 9.2 mm Hg for peak SeDBP and 12.9 mm Hg for peak SeSBP (reduction over placebo). An irbesartan dose of 150 mg once daily should produce peak seated blood pressure reductions of $\approx 10/7$ mm Hg over placebo. An irbesartan dose of 300 mg once daily should produce corresponding reductions of $\approx 11/8$ mm Hg. As with trough blood pressure, only modest additional benefit would be expected with irbesartan doses beyond 300 to 600 mg. Table 3 shows that the T:P ratio for SeDBP is generally $>60\%$ with once-daily doses of 150 mg and above. When measured by ambulatory blood pressure monitoring, the placebo-adjusted T:P ratio with irbesartan 150 mg once daily was 74% for DBP and 66% for SBP.⁹

These results from the primary analysis were confirmed by the LOCF analysis (see “Methods” and “Allocation of Pa-

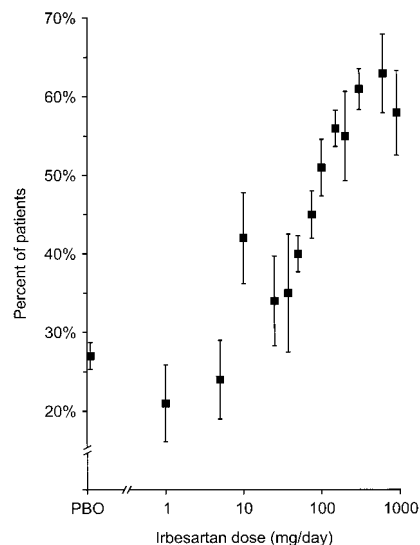


Figure 3. Percentage of patients achieving a therapeutic response (trough SeDBP <90 mm Hg or a reduction from baseline of ≥ 10 mm Hg) by irbesartan dose.

tients to Study Groups” sections for further details). With the Hill coefficient set at 1, E_{\max} was calculated as 7.34 mm Hg, and D_{50} , 66.4 mg for trough SeDBP. For trough SeSBP, the corresponding values were 12.5 mm Hg and 76.7 mg, respectively. The more general model also produced results similar to the original analyses.

Therapeutic Response

Figure 3 shows the dose-response relationship for the percentage of patients achieving a favorable therapeutic response (trough SeDBP <90 mm Hg or a reduction from baseline of ≥ 10 mm Hg). Fifty-six percent of patients are predicted to respond favorably to irbesartan 150 mg once daily; the percentage of patients responding plateaus at doses >300 mg. The D_{50} for therapeutic response is ≈ 75 mg daily.

Heart Rate Effects

In each individual study, there were no clinically or statistically significant changes in heart rate with any irbesartan dose or with placebo at either peak or trough (data not shown).

Discussion

Data from 2955 patients with mild to moderate hypertension who were enrolled in eight multicenter, randomized, double-blind, placebo-controlled studies were pooled to analyze the integrated efficacy of irbesartan across the dose range of 1 mg to 900 mg. Testing over this 900-fold range of doses was possible because of the excellent safety profile of irbesartan, including a lack of dose-limiting side effects, even at the highest doses tested.¹³ Irbesartan showed a clear dose-response relationship for both a reduction in blood pressure and the percentage of patients who achieved a therapeutic response. The no-effect irbesartan dose appears to be <10 mg daily, and the maximal-effect dose appears to be ≈ 300 mg daily. Consistent and clinically significant reductions in trough SeDBP (ie, a >4 mm Hg reduction versus placebo)

TABLE 3. T:P Ratios in Placebo-Controlled Irbesartan Monotherapy Studies*

Protocol Number	Time, Week	Dose, mg Once Daily	n	Office SeDBP Change From Baseline		
				Trough, mm Hg†	Peak, mm Hg†	Placebo-Adjusted T:P Ratio, %
002	8	50	73	-2.83	-4.38	65
		100	69	-3.22	-4.46	72
025	8	100	66	-4.13	-7.07	58
		200	67	-4.40	-7.06	62
		300	70	-5.79	-8.35	69
029	6	75	92	-5.11	-7.37	69
		150	85	-5.97	-8.25	72
	12	75	93	-3.74	-7.10	53
037	8‡	37.5	38	-3.44	-6.39	54
		100	33	-5.97	-9.47	63
		300	39	-6.15	-11.12	55
038	12	75	115	-3.17	-5.06	63
		150	118	-3.86	-5.98	64
050	8	150	87	-5.07	-7.15	71
		300	86	-5.11	-7.19	71
		600	84	-6.32	-9.74	65
		900	77	-4.92	-7.13	69

*T:P ratios were determined in six of the eight studies.

†Adjusted mean difference from placebo (ie, placebo subtracted).

‡Peak represents the maximum mean hourly value for blood pressure reduction in each treatment group.

and suitable T:P ratios were achieved with once-daily irbesartan doses of ≥ 150 mgr. Reductions in DBP of this magnitude are associated with reduced risk of stroke, coronary heart disease, and death.¹⁵

The antihypertensive dose-response relationship demonstrated in this integrated analysis is supported by pharmacodynamic data, which show that irbesartan also has a dose-related effect on the renin-angiotensin system in humans. Single doses of irbesartan produced dose-related increases in plasma Ang II and plasma renin activity as well as a dose-related blunting of the pressor effect of exogenous Ang II.^{3,5,16}

The dose-related efficacy of irbesartan has clinical implications. In one of the included studies, the effects of titration were assessed by an elective titration design in which patients were titrated or not according to blood pressure response after week 6.⁷ Once-daily treatment with irbesartan 75 mg titrated as needed to 150 mg and 150 mg titrated as needed to 300 mg significantly reduced SeDBP and SeSBP at week 12 ($P < 0.01$ for each treatment group versus placebo). There were further decreases from week 6 to week 12 in both groups, and a greater effect was observed with 150 mg titrated to 300 mg than with 75 mg titrated to 150 mg. Both irbesartan regimens had a tolerability profile similar to that of placebo. This study demonstrated that initiation of irbesartan at 150 mg once daily and titrating to 300 mg once daily, if necessary, represents an efficient regimen for managing patients with mild to moderate hypertension. Thus, the E_{\max} prediction of enhanced effect with titration has been confirmed for irbesartan.

Full 24-hour blood pressure control was demonstrated by SeDBP T:P ratios of 60% to 70% with irbesartan doses of ≥ 150 mg in individual studies. The appropriateness of once-daily dosing was confirmed by 24-hour ambulatory blood pressure data obtained in one of the included studies, which showed that irbesartan doses of 150 mg once daily or in a divided dose (75 mg twice daily) produced equivalent reductions in diastolic and SBP over the full 24-hour dosing interval.⁹

In conclusion, once-daily irbesartan demonstrates a predictable dose-related antihypertensive effect over the therapeutic dose range, with once-daily doses of ≥ 150 mg providing clinically significant blood pressure lowering.

Acknowledgments

Financial support for these studies was provided by Bristol-Myers Squibb Pharmaceutical Research Institute and Sanofi. The authors thank the clinicians and patients who provided the data in the eight individual studies.

References

1. Cazaubon C, Gougat J, Bousquet F, Guiraudou P, Gayraud R, Lacour C, Roccon A, Galindo G, Barthelemy G, Gautret B, Bernhart C, Perreaut P, Breliere J-C, Le Fur G, Nisato D. Pharmacological characterization of SR 47436, a new nonpeptide AT₁ subtype angiotensin II receptor antagonist. *J Pharmacol Exp Ther*. 1993;265:826-834.
2. Necciarri J, Denolle T, Le Coz F, Donazzolo Y, Pastor G, Sissmann J. Pharmacokinetics of SR 47436 (BMS 186295), a new angiotensin II receptor antagonist in man. *J Hypertens*. 1994;12:88. Abstract.
3. Ribstein J, Sissmann J, Picard A, Bouroudian M, Mimran A. Effects of the angiotensin II antagonist SR 47436 (BMS 186295) on the pressor response to exogenous angiotensin II and the renin-angiotensin system in sodium replete normal subjects. *J Hypertens*. 1994;12:131. Abstract.

4. Timmermans PBMWM, Smith RD. Angiotensin II receptor subtypes: selective antagonists and functional correlates. *Eur Heart J*. 1994; 15(suppl D):79–87.
5. Sissmann J, Bouroudian M, Armagnac C, Donazollo Y, Latreille M, Panis R. Angiotensin II blockade in healthy volunteers: tolerability and impact on renin angiotensin system components of single and repeated doses of a new angiotensin II receptor antagonist SR 47436 (BMS 186295). *J Hypertens*. 1994;12:S92. Abstract.
6. Pool JL, Guthrie RM, Littlejohn TW III, Raskin P, Shepherd A, Weber MA, Weir MR, Wilson TW, Wright J, Kassler-Taub KB, Reeves RA. Dose-related antihypertensive effects of irbesartan in patients with mild-to-moderate hypertension. *Am J Hypertens*. 1998. In press.
7. Guthrie R, Saini R, Herman T, Pleskow W, Sprecher D, Collins G. Efficacy and safety of irbesartan, the angiotensin II receptor antagonist, in essential hypertension. *Clin Drug Invest*. 1998;15:217–227.
8. Fogari R, Ambrosoli S, Corradi L, Degli Esposti E, Mos L, Nami R, Nicrosini F, Pessina AC, Salvetti A, Vaccarella A, Zanchetti A, Martin A, Reeves RA. 24-Hour blood pressure control by once-daily administration of irbesartan assessed by ambulatory blood pressure monitoring. *J Hypertens*. 1997;15:1511–1518.
9. Kassler-Taub K, Littlejohn T, Elliott W, Ruddy T, Adler E. Comparative efficacy of two angiotensin II receptor antagonists, irbesartan and losartan, in mild-to-moderate hypertension. *Am J Hypertens*. 1998. In press.
10. Peto R, Collins R, Gray R. Large-scale randomized evidence: large, simple trials and overviews of trials. *J Clin Epidemiol*. 1995;48:23–40.
11. Swales JD. Meta-analysis as a guide to clinical practice. *J Hypertens*. 1993;11(suppl 5):S59–S63.
12. Johnston GD. Dose-response relationships with antihypertensive drugs. *Pharmacol Ther*. 1992;55:53–93.
13. Simon TA, Gelarden RT, Freitag SA, Kassler-Taub KB, Davies R. The safety of irbesartan in the treatment of mild-to-moderate hypertension: results of nine randomized, double-blind, placebo-controlled studies. *Am J Cardiol*. 1998. In press.
14. Lalonde RL. Pharmacokinetic-pharmacodynamic relationships of cardiovascular drugs. In: Derendorf H, Hochhaus G, eds. *Handbook of Pharmacokinetic/Pharmacodynamic Correlation*. Boca Raton, Fla: CRC Press; 1995:197–225.
15. Collins R, Peto R, MacMahon S, Hebert P, Fiebach NH, Eberlein KA, Godwin J, Qizilbash N, Taylor JO, Hennekens CH. Blood pressure, stroke, and coronary heart disease, part 2: short-term reductions in blood pressure: overview of randomised drug trials in their epidemiological context. *Lancet*. 1990;335:827–838.
16. Hagmann M, Burnier M, Nussberger J, Leenhardt AF, Brouard R, Waeber B, Brunner HR. Natriuretic and hormonal effects of SR 47436 (BMS 186295), a new angiotensin II receptor antagonist in normotensive volunteers. *Am J Hypertens*. 1994;7:13A. Abstract.
17. Kochar M, Guthrie R, Triscari J, Kassler-Taub K, Reeves RA, Pulchalski J, Nichola P, Gelarden RT. Irbesartan in combination with hydrochlorothiazide in mild-to-moderate hypertension. *Am J Hypertens*. 1997;10(4 pt 2):106A. Abstract.
18. Weber M, Saini R, Kassler-Taub K, Reggi D, Ferdousi T, Nalence A. Irbesartan combined with low-dose hydrochlorothiazide for mild-to-moderate hypertension. *J Hypertens*. 1998. In press. Abstract.