Review Paper

The Risks and Benefits of Initial Irbesartan/Hydrochlorothiazide Combination Therapy in Patients With Severe Hypertension

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*The impact of delays in blood pressure (BP) reduction is particularly relevant for patients with severe hypertension who are at risk for hypertensive emergencies. Combination therapies may hold promise as initial treatment for these patients. The safety and efficacy of initial irbesartan/hydrochlorothiazide (angiotensin receptor blocker/thiazide) treatment was compared with that of irbesartan as monotherapy in a multicenter, double-blind, parallel-group study in patients with severe hypertension. After 5 weeks, 47% of patients receiving combination therapy achieved a target diastolic BP <90 mm Hg compared with 33% with monotherapy (*P=.*0005). Similarly, systolic BP/diastolic BP <140/90 mm Hg targets were reached by more subjects treated with combination therapy than subjects receiving monotherapy (34.6% vs 19.2%,* P<.*0001). Initial use of combination therapy instead of monotherapy is estimated to prevent between 250 and 4500 cardiovascular events in every 100,000 severely hypertensive patients over 5 years, without significantly increasing serious adverse event rates.* J Clin Hypertens (Greenwich). *2009;11:277–283.* ©*2009 Wiley Periodicals, Inc.*

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In patients with severe hypertension, the short-term risk of hypertensive emergencies, including hospitalization for extremely elevated levels of blood pressure (BP), chronic heart failure, intracranial hemorrhage, progression of hypertensive retinopathy and nephropathy, and rupture of aneurysms, is substantial.[1–4] Hypertensive crises are believed to occur at a rate of one in 5–10 patient-years of exposure to severe hypertension.[1,2] The impact of delays in BP reduction is particularly relevant in this patient population.

Severe hypertension is still prevalent today and is associated with substantial morbidity and mortality.[3–5] One-year event rates are higher in severely hypertensive patients compared with patients with mild to moderate hypertension and cumulative cardiovascular event rates, for this population, increase dramatically over time.[5]

Recently, a body of clinical trial experience has revealed important advantages to more aggressive approaches to treatment.[6,7] Two or 3 therapies prescribed from the start of treatment, for example, were significantly more efficacious than gradual titration and add-on strategies.[6,7]

Recently the US Food and Drug Administration evaluated pivotal data for initial combination therapy with irbesartan/hydrochlorothiazide (HCTZ) for patients with severe hypertension and requested

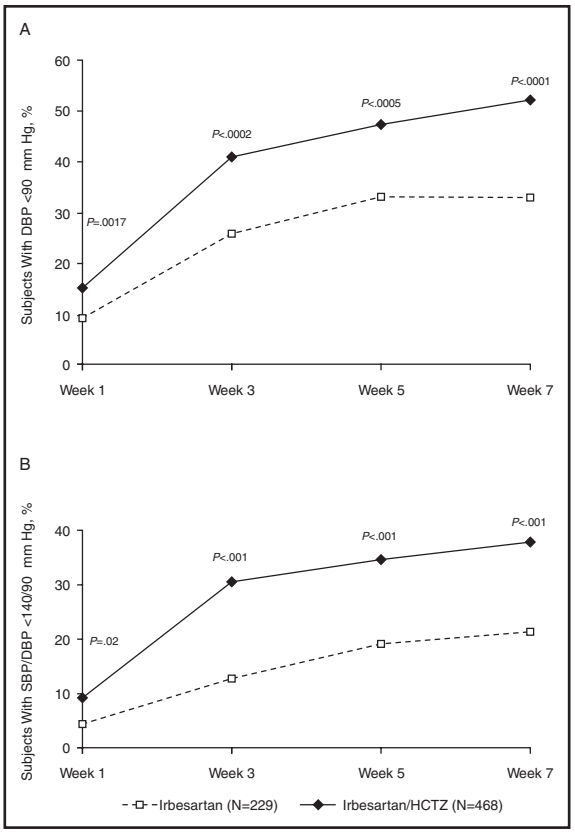

Figure 1. Blood pressure (BP) control in severely hypertensive patients after treatment with irbesartan or irbesartan/hydrochlorothiazide (HCTZ). Percentage of patients achieving (A) diastolic BP (DBP) <90 mm Hg; (B) systolic BP (SBP)/DBP <140/90 mm Hg after treatment with irbesartan or irbesartan/HCTZ. The primary efficacy endpoint was DBP <90 mm Hg at 5 weeks. Adapted with permission from Neutel et al.[8]

a quantitative benefit/risk analysis. This review presents the benefit/risk analysis in the context of current guidelines and the relevance to practicing physicians.

EFFICACY OF INITIAL IRBESARTAN/HCTZ COMBINATION THERAPY FOR THE TREATMENT OF SEVERE HYPERTENSION: THE PIVOTAL TRIAL

The safety and efficacy of irbesartan/HCTZ as initial treatment of severe hypertension were evaluated in a multicenter, double-blind, active-control, 7-week, parallel-group study in patients with severe hypertension who were uncontrolled on monotherapy (diastolic BP [DBP] ≥110 mm Hg).[8] Following a 1-week placebo lead-in period, patients were randomized in a 2:1 ratio to receive fixed-dose irbesartan/HCTZ combination therapy (150 mg/12.5 mg forced titration to 300 mg/25 mg after 1 week) or irbesartan monotherapy (150 mg forced titration to 300 mg after 1 week). This 2-step rapid titration scheme was developed to lower the risk of adverse events due to sudden BP lowering and at the same time to avoid unnecessary exposure to severe hypertension due to suboptimal drug doses. The primary objective was to compare the proportion of subjects whose DBP was controlled at week 5 (DBP >90 mm Hg). Calculation of sample size and power of the test was based on the Fisher exact test performed at a 2-sided 5% level of significance.[8]

Subjects were mostly middle aged (mean age of 52.5 years) and Caucasian (84%).[8] Subjects had a history of hyperlipidemia (34%), diabetes mellitus (12%), stable angina pectoris (3%), transient ischemic attack or stroke (2%), and myocardial infarction (1%). Baseline hypertension was severe with a baseline systolic BP (SBP)/DBP of 172/113 mm Hg. The mean duration of hypertension was 7 years.

Better, Faster Control With Combination Therapy: Efficacy Data

As expected, this study demonstrated that initial irbesartan/HCTZ combination therapy provided clinically relevant benefits over monotherapy in the treatment of patients with severe hypertension.[8] The results are similar to those noted in other studies where combination therapy is more effective than monotherapy.

More patients responded to combination therapy than to irbesartan alone (Figure 1).[8] Forty-seven percent of patients receiving combination therapy achieved a target DBP <90 mm Hg at week 5 compared with 33% with monotherapy (*P*=.0005). Similarly, SBP/DBP <140/90 mm Hg targets were reached by more subjects treated with combination therapy than those who received monotherapy (34.6% vs. 19.2% at week 5, *P*<.0001).

Again, as expected, combination therapy reduced BP more than irbesartan therapy alone (Figure 2).[8] At week 5, the mean decreases from baseline in SBP/DBP were 31/24 mm Hg and 21/19 mm Hg for the combination and monotherapy arms, respectively (*P*<.0001). These data translate into a mean difference between groups of 10/5 mm Hg. For most subjects, these BP reductions meant a change from the severe to the moderate hypertension category (Figure 3). At week 5, only 1.7% of patients receiving combination therapy continued to have severe high BP compared with 6.1% of patients receiving monotherapy (*P*=.004). In addition, over the course of 7 weeks of treatment, the probability of having an episode of DBP

≥110 mm Hg at least once was 24.9% with monotherapy and 16.4% with combination therapy.

Combination therapy also took effect rapidly. As early as 1 week after the start of treatment, significantly fewer patients taking irbesartan/HCTZ combination therapy (12.8%) continued to have severely high BP compared with patients taking irbesartan monotherapy (18.8%, *P*=.04; Figure 3).

In summary, in this study, for every 12 patients treated with combination therapy rather than monotherapy, one case of recurrent DBP ≥110 mm Hg was avoided. Furthermore, for every 100 patients treated with combination therapy, at least 26 fewer weeks of exposure to severe hypertension were experienced than with monotherapy (*P*=.004).

Clinical Relevance: Discussion of the Efficacy Data

Benefits of rapid BP reduction in severely hypertensive patients, as seen in this irbesartan/HCTZ program, are two-fold. In the short term, hypertensive emergecies, such as encephalopathy, retinopathy, nephropathy, cardiomyopathy, and hemorrhages, are more likely to be avoided. In the intermediate to long term, cardiovascular events such as myocardial infarction, stroke, and cardiovascular death could be reduced.

The overall 10/5 mm Hg difference in BP between the irbesartan/HCTZ and irbesartan groups is clinically relevant. In both observational and clinical studies, 5 mm Hg decreases in DBP were associated with continuous and independent decreases in stroke rates of 34%–42%.[9,10] In patients with type 2 diabetes, each 10 mm Hg decrease in SBP was associated with reductions in risk of 12% for diabetes-related complications, 15% for diabetes-related deaths, 11% for myocardial infarctions, and 13% for microvascular complications.[11] Since physicians are slow to adjust medication, in an add-on scheme patients may not benefit from the additional 10/5 mm Hg reduction in BP attributable to HCTZ for a year or more.

The more rapid BP-lowering effects in the combination group compared with the monotherapy group are also clinically relevant. The importance of prompt reduction of severe hypertension has been known for many years.[1,2] In the 1967 Veterans Administration Cooperative[1] study, investigators reported 27% fewer cardiovascular events with initial combination therapy vs placebo when DBP was reduced from severe (115–129 mm Hg) to more moderate levels (reduction of 30 mm Hg) within 2 months of treatment. More recently, in less severe populations in the Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) trial,

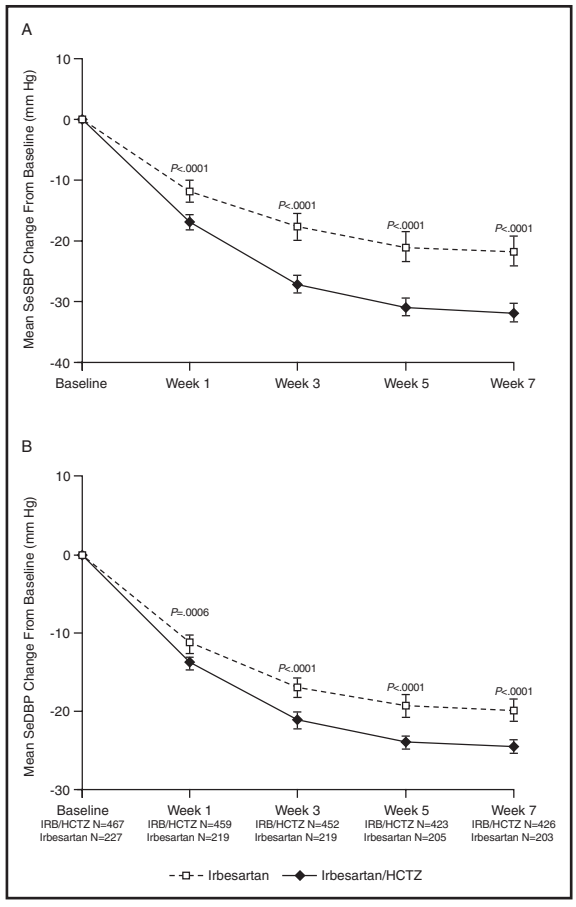

Figure 2. Changes in blood pressure over time in severely hypertensive patients after treatment with irbesartan or irbesartan (IRB)/hydrochlorothiazide (HCTZ). Reproduced with permission from Neutel et al.[8] SeSBP indicates seated systolic blood pressure; SeDBP seated diastolic blood pressure.

SBP normalization after 6 months of treatment was associated with reduced stroke, myocardial infarction, and cardiovascular mortality (45%, 14%, and 21%, respectively).[12] Other trials suggest that delays of as little as 1 month in starting antihypertensive therapy in high-risk individuals can significantly increase the risk of certain cardiovascular events.[6,13]

Longer term trials have shown that sustained reductions in BP are consistently associated with better long-term outcomes.[1,2,14–17] In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), 2 mm Hg differences in SBP over 5 years of treatment with chlorthalidone compared to lisinopril resulted in a 15% difference in stroke rates.[16] In the Study on Cognition and Prognosis in the Elderly (SCOPE), 3.5 years of candesartan treatment led to a 28% reduction in stroke rates compared with control

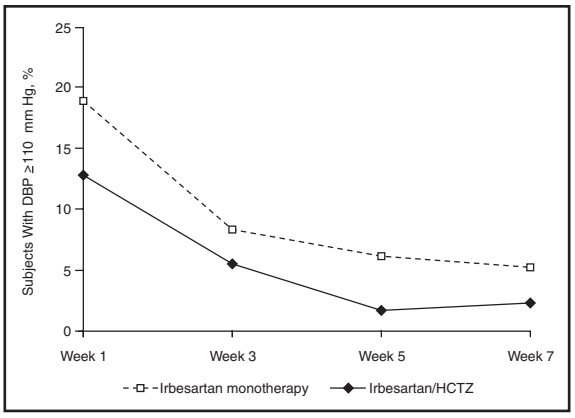

Figure 3. The proportion of patients with diastolic blood pressure (DBP) ≥110 mm Hg over time after treatment with irbesartan or irbesartan/hydrochlorothiazide (HCTZ).

treatment,[17] and in the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), 5.5 years of the amlodipine-based regimen reduced stroke rates by 23%.[15]

Lastly, these results are consistent with other studies using combination antihypertensive medication. In previous trials, combination therapy reduced BP more than either of its constituents prescribed separately and the efficacy of the 2 components was approximately additive when they were given in combination.[18,19] Irbesartan/HCTZ combination therapy has also been used effectively in difficult to treat patients.[20,21] In the large Irbesartan/Hydrochlorothiazide Blood Pressure Reductions in Diverse Patient Populations (INCLUSIVE) trial, 30% of patients had diabetes mellitus, 48% of patients had hyperlipidemia and baseline SBPs ranging from 130 to 180 mm Hg.[22] In this cohort of mixed severities, 77% of patients achieved their SBP goal; 83% achieved their DBP goal (<90 mm Hg; <80 mm Hg for type 2 diabetes mellitus); and 69% achieved their SBP/DBP goal after 18 weeks of sequential antihypertensive therapy (HCTZ 12.5 mg for 2 weeks, irbesartan/HCTZ 150/12.5 mg for 8 weeks, then irbesartan/HCTZ 300/25 mg for 8 weeks).[22]

SAFETY OF INITIAL IRBESARTAN/HCTZ COMBINATION THERAPY FOR THE TREATMENT OF SEVERE HYPERTENSION

Safety Data

As discussed earlier, use of irbesartan/HCTZ as initial treatment in severely hypertensive patients depends on the benefit/risk ratio. Not only do the efficacy benefits have to be significant, but safety risks associated with the initial addition of HCTZ need to be minimal.

This study was prospectively designed to evaluate the 2 main safety concerns surrounding angiotensin receptor blocker (ARB)/HCTZ treatment. First, the initial BP response may be so great that orthostatic hypotension and syncope may ensue. Second, some patients may be unnecessarily exposed to rare adverse events due to 12.5 mg or 25 mg doses of HCTZ. In particular, prespecified adverse events (hypotension, dizziness, syncope, headaches, hypokalemia, and hyperkalemia) were carefully monitored.

The overall frequency of adverse events during the 7 weeks of treatment was lower in the irbesartan/HCTZ therapy group than in the irbesartan group (Table).[8] The majority of adverse events were mild to moderate and unrelated to treatment. Fewer patients in the combination therapy group experienced the prespecified adverse events than in the monotherapy group (8.8% vs. 11.5%, respectively). Headache was the most frequently reported prespecified adverse event (4.3% with combination therapy and 6.6% with monotherapy).

Hyperkalemia and hypokalemia (defined by the investigator according to clinical relevance) occurred slightly more frequently in the irbesartan/HCTZ group (0.2% and 0.6%, respectively) than in the irbesartan group (0% and 0.4%, respectively). Hypotension and dizziness occurred with similar frequency in both groups. Hypotension was rare with an incidence of 0.6% in the irbesartan/HCTZ group and 0% in the irbesartan group. No cases of syncope were observed. The minimum SBP for the entire study was 99 mm Hg at week 7. Study medication was well tolerated with very few discontinuations due to adverse events in either group (1.9% with combination therapy and 2.2% with monotherapy).

Clinical Context: Discussion of the Safety Data

In this 7-week trial, no evidence of excess risk for irbesartan/HCTZ compared with irbesartan could be detected. The only common adverse event that seemed to be related to the addition of HCTZ was hypokalemia, which is a well documented and easy to manage effect of nonpotassium sparing diuretics. Though hypokalemia was observed in 0.6% of subjects, serum potassium levels <3.0 mmol/L were not observed. Data from other studies suggest that the hypokalemic effects of HCTZ were most likely attenuated by the hyperkalemic effects of irbesartan. In a matrix study of irbesartan (0, 37.5, 100, and 300 mg) and HCTZ (0, 6.25, 12.5, and 25 mg), hypokalemia associated with 25 mg of HCTZ was reduced with increasing doses of

Table. Incidence of Adverse Events (All Randomized Patients) Following Initial Treatment of Severely Hypertensive Patients for 7 Weeks

Adverse Events (AEs), n (%)	Irbesartan/ HCTZ Combination Therapy (n=468)	Irbesartan Monotherapy (n=229)
Total	140 (29.9)	82 (36.1)
Prespecified	41 (8.8)	26 (11.5)
Dizziness	17 (3.6)	9 (4.0)
Headache	20 (4.3)	15 (6.6)
Hyperkalemia/increased potassium	1 (0.2)	0
Hypokalemia/decreased potassium	3 (0.6)	1 (0.4)
Hypotension	3 (0.6)	0
Serum potassium<3.0 mmol/L	0	0
Serum potassium>6.0 mmol/L	3 (0.6)	3 (1.3)
Serious	1 (0.2)	1 (0.4)
Deaths	0	0
Discontinuations due to AE	9 (1.9)	5 (2.2)

Abbreviation: HCTZ, hydrochlorothiazide. Adapted with permission from Neutel et al.[8]

irbesartan.[18] Overall, irbesartan is believed to ameliorate the dose-related biochemical abnormalities associated with HCTZ.

Despite the slight increase in risk of hypokalemia, the long-term risk of renal complications with initial irbesartan/HCTZ treatment is believed to be low due to the positive effects of ARBs on renal function. ARBs, including irbesartan, have been associated with improved renal outcomes. For example, in patients with diabetes, hypertension, and microalbuminuria enrolled in the Irbesartan Microalbuminuria II trial (IRMA II), treatment with 300 mg of irbesartan significantly slowed the progression of microalbuminuria to overt nephropathy when compared with placebo ($P<.001$).[23] In addition, in long-term studies, diuretics have been used safely as concomitant medications in patients treated with irbesartan or losartan for the prevention of renal disease.[24,25] Lastly, in another study, diuretics were shown to provide additional reductions in proteinuria and albuminuria when prescribed on top of ARBs.[26]

Although high doses of diuretics carry a risk of insulin resistance,[27] in long-term studies, ARBs delay the onset of diabetes in hypertensive patients.[28–30] In subjects with diabetes and hypertension, for example, irbesartan improved lipid, blood glucose, and hemoglobin A_{1c} levels.[31] Furthermore, it has been suggested that the combination of an ARB, which downregulates the renin-angiotensin system thereby reducing damage to the kidney, and a diuretic, which reduces sodium retention, could be particularly beneficial in hypertensive diabetic patients, which constitute a particularly difficult to treat population. In the INCLUSIVE trial, more than 50% of type 2 diabetes patients treated with combination irbesartan/HCTZ reached their SBP goals and 40% reached their SBP/DBP goals (<130/80 mm Hg).[32]

Other safety concerns with HCTZ include extremely rare events like pancreatitis and severe allergic reactions (eg, interstitial pneumonitis).[33] Because this trial was short, such events were not observed. However, they have been evaluated through postmarketing surveillance of second-line use of irbesartan/HCTZ. With the exception of hypokalemia, numbers of cases per 1 million patient-years of exposure were lower for irbesartan/HCTZ than for irbesartan alone: 1.3 vs 2.1 for pancreatitis, 6.8 vs 21.3 for renal failure, 3.2 vs 7.4 for syncope, 7.8 vs 11.0 for allergic reactions, 0.1 vs 0.7 for interstitial pneumonitis, and 2.7 vs 2.0 for hypokalemia. Although these postmarketing surveillance event rates are based on second-step use of irbesartan/HCTZ and on drug sales to wholesalers (17.7 million treatment years for irbesartan and 6.8 million patient treatment years for irbesartan/HCTZ) and therefore should be interpreted with caution, they are consistent with the safety profile in previous trials and in the original New Drug Application.[18–21]

Poor compliance is an especially common problem with severe hypertension. Self-reported poor compliance is associated with almost twice the likelihood of presentation to the emergency room for severe hypertension.[34] Since studies have also shown that a single combination pill is associated with better compliance than the simultaneous

prescription of the 2 separate components,[35] a good tolerability profile associated with simple posology suggests better patient compliance.

Lastly, these data are consistent with safety data collected from other ARB/HCTZ combination therapies. In a metaanalysis of trials comparing combination products with monotherapy, ARBs showed no relationship between dose and the total proportion of patients reporting adverse events.[36] By contrast, doubling the diuretic dose (from half-standard to standard) increased adverse events five-fold (from approximately 2%–10% more than placebo).

OVERALL BENEFIT/RISK RATIO ASSESSMENT

For the purpose of the formal review of irbesartan/HCTZ for indication as initial therapy in patients with severe hypertension, a post hoc benefit risk analysis based on 100,000 patients and a 5-year treatment period was performed. Estimates suggest that combination treatment prevented 50–100 hypertensive crises, 50–100 cardiovascular events during the initial 5-week treatment period, and 250–4500 cardiovascular events during the remaining 5 years. By contrast, zero to a few serious complications would be expected due to diuretic therapy; the risk of pancreatitis and interstitial pneumonitis were both between zero and 5 cases. Although formal estimates of benefit/risk are limited by the fact that they are imprecise, in this program the benefits and risks are separated by orders of magnitude. Thus, overall, it was concluded that the benefits of initial treatment with irbesartan/HCTZ compared with irbesartan significantly outweighed risks associated with the addition of HCTZ.

CONCLUSION

Initial use of irbesartan/HCTZ instead of irbesartan has the potential to prevent between 250 and 4500 cardiovascular events in every 100,000 severely hypertensive patients over 5 years, without significantly increasing serious adverse event rates. Because of the urgency associated with lowering BP in severely hypertensive patients, this positive benefit/risk profile has led to expanded labeling that now incorporates initial irbesartan/HCTZ use for moderate to severe hypertensive patients.

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