Divergent Results Using Clinic and Ambulatory Blood Pressures

Report of a Darusentan-Resistant Hypertension Trial

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Abstract—Patients with resistant hypertension are at increased risk for cardiovascular events. The addition of new treatments to existing therapies will help achieve blood pressure (BP) goals in more resistant hypertension patients. In the current trial, 849 patients with resistant hypertension receiving ≥3 antihypertensive drugs, including a diuretic, at optimized doses were randomized to the selective endothelin A receptor antagonist darusentan, placebo, or the central α-2 agonist guanfacine. The coprimary end points of the study were changes from baseline to week 14 in trough, sitting systolic BP, and diastolic BP measured in the clinic. Decreases from baseline to week 14 in systolic BP for darusentan (-15 ± 14 mm Hg) were greater than for guanfacine (-12 ± 13 mm Hg; $P<0.05$) but not greater than placebo (-14 ± 14 mm Hg). Darusentan, however, reduced mean 24-hour systolic BP (-9 ± 12 mm Hg) more than placebo (-2 ± 12 mm Hg) or guanfacine (-4 ± 12 mm Hg) after 14 weeks of treatment ($P<0.001$ for each comparison). The most frequent adverse event associated with darusentan was fluid retention/edema at 28% versus 12% in each of the other groups. More patients withdrew because of adverse events on darusentan as compared with placebo or guanfacine. We conclude that darusentan provided greater reduction in systolic BP in resistant hypertension patients as assessed by ambulatory BP monitoring, in spite of not meeting its coprimary end points. The results of this trial highlight the importance of ambulatory BP monitoring in the design of hypertension clinical studies. **(*Hypertension*. 2010;56: 824-830.)**

Key Words: endothelin ■ hypertension ■ resistant hypertension ■ endothelin antagonist

Treatment guidelines for hypertension recommend a blood pressure (BP) of <140/90 mm Hg for most patients (<130/80 mm Hg for patients with comorbidities).[1,2] The objective of reaching this goal is reduction of cardiovascular and renal events. Many patients can achieve this BP target with 1 or 2 antihypertensive drugs in addition to appropriate lifestyle changes. However, patients with treatment-resistant hypertension (RHTN) require full doses of ≥3 medications that act by complementary mechanisms, including a diuretic, to achieve these BP goals,[1,3] and often this is not enough. There are many reasons for failure to achieve BP targets, including poor adherence to treatment regimens by the patient, inexpertly selected treatment regimens, or conflicting effects of concomitantly administered drugs.[3–5]

Patients with treatment RHTN typically have other cardiovascular risks, such as obesity, diabetes mellitus (DM), and chronic kidney disease (CKD). Few prospective clinical trials have investigated treatment strategies in patients with treatment RHTN, and most have been largely empirical and uncontrolled.[6–8]

Endothelin receptor antagonists (ERAs) are useful to reduce BP in people with hypertension. Previous studies with the nonselective, sulfonamide-type ERA, bosentan, produced significant reductions in systolic (SBP) and diastolic (DBP) pressures, similar to those observed with an angiotensin-converting enzyme inhibitor in patients with hypertension.[9] Darusentan, a propanoic acid-based endothelin type A-selective receptor antagonist, as a single agent dosed at 100 mg daily, decreased BP by ≈11/8 mm Hg, corrected for the placebo response, after 6 weeks in patients with stage 1 or 2 hypertension.[10] Results of a recently published randomized, double-blind trial comparing differing doses of darusentan with placebo in patients with treatment RHTN demonstrated superiority of darusentan over placebo for achieving BP

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This trial has been registered at www.clinicaltrials.gov (identifier NCT00389779).

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goal.[11] The current article presents the results of a second randomized, double-blind placebo controlled study in patients with treatment RHTN, unable to achieve BP goal on ≥3 different antihypertensive medications, including a diuretic, at optimized dosages.

Methods

Patients

Patients were recruited from 240 sites in North and South America, Europe, New Zealand, and Australia. Patients were eligible to participate if they had treatment RHTN defined as an SBP of ≥140 mm Hg (≥130 mm Hg if they had DM or CKD) despite treatment with ≥3 antihypertensive drugs from different drug classes, including a diuretic, at optimized doses. A minimum dose of 25 mg per day of hydrochlorothiazide (or its equivalent for other thiazide diuretic drugs) was required. Patients were also required to have a body mass index between 20 and 43 kg/m^2, and an estimated glomerular filtration rate of ≥30 mL/min per 1.73 m^2. Women were required to be of nonchildbearing potential. Patients with sitting SBP of ≥180 mm Hg or DBP ≥110 mm Hg, heart failure (HF), poorly controlled DM, anemia, sleep apnea, liver dysfunction, or a history of coronary, arrhythmic, or stroke events within the past 6 months were excluded from study participation. All of the patients provided written informed consent. The ethics committees or institutional review boards of all of the participating sites approved the protocol. The trial was undertaken in compliance with Good Clinical Practice guidelines and the ethics principles set out in the Declaration of Helsinki.

Study Design

After screening for eligibility, all of the patients underwent a single blind, placebo run-in for 2 weeks to ensure that BP remained stable and continued to meet entry criteria. Eligible patients were randomly assigned in a ratio of 3:1:3 to darusentan (optimized dosing at 50, 100, or 300 mg according to investigator discretion), placebo, or guanfacine (1 mg) orally, once daily in the morning. According to the protocol, study drug was to be up-titrated until the patient met SBP goal and experienced a drop in SBP of ≥10 mm Hg, unless there was a specific safety concern.

A group external to the study sponsor generated the randomization schedule, and all of the individuals involved in the conduct of the trial were blinded to treatment assignments for the duration of the study. Randomized patients were stratified by comorbidity status (presence of DM or CKD versus absence of both) and race (black versus nonblack). Randomization assignments were made centrally via an automated telephone system. The pregenerated randomization schedule was programmed via algorithm into the telephone system. Investigational sites were required to call directly into the telephone system to randomize eligible patients, which occurred at the appropriate visit based on demographic data entered into the system by the site, and to receive assignments of blinded study drug at each visit. Clinical supplies were overencapsulated and packaged in blister packs identically for each treatment group, according to the randomization algorithm. Changes to background antihypertensive therapy were not allowed during the study; however, investigators could increase the use of diuretic drugs to treat edema or other fluid-related adverse effects.

The prespecified coprimary end points were the changes from baseline to week 14 in sitting SBP and DBP. Secondary end points included changes from baseline to final measurement in mean 24-hour BPs, the percentage of patients who achieved SBP goal (<140 mm Hg or <130 mm Hg in patients with DM or CKD) after 14 weeks of treatment, and change from baseline in estimated glomerular filtration rate. The safety and tolerability of darusentan in the patient population were also examined.

BP Measurements

Site personnel involved in the conduct of this study were specially trained and certified by an external vendor (Shared Care, Inc) to take clinic BP readings consistent with the study protocol. Clinic BPs were measured at each study visit at lowest study drug concentration (ie, trough) in the seated position (for ≥5 minutes) by standard sphygmomanometry. Three consecutive measurements were obtained, each separated by ≈2 minutes, and these values were averaged to determine the patient's BP at each visit for the purpose of analysis. Ambulatory BP monitoring was completed at randomization and at the end of the study. At each assessment, automated readings were obtained every 20 minutes over a 24-hour interval. Mean 24-hour measurements were obtained by averaging BP readings collected within a clock hour and then averaging across available clock hours during the 24-hour monitoring period for each patient. All of the ambulatory records were evaluated for quality according to prespecified criteria.

Laboratory Assessments

Laboratory tests were performed at baseline, after 2 weeks, and every 4 weeks thereafter. Estimated glomerular filtration rate was calculated using an abbreviated form of the Modified Diet in Renal Disease equation[12] at screening (for entry purposes), baseline, and end of study. Safety electrocardiograms were collected periodically throughout the study. Adverse events and study drug compliance were assessed at every visit.

Statistical Analyses

The planned sample size of 110 placebo, 330 darusentan, and 330 guanfacine patients was sufficient to detect a difference between darusentan and placebo with >95% power; between placebo and guanfacine (superiority) with 93% power; and a difference between darusentan and both control treatments using a fixed sequence approach with 92% power. Calculations assumed an 8-mm Hg difference in change from baseline to week 14 in trough SBP for the comparison of darusentan to placebo and a 4-mm Hg difference for the comparison of darusentan to guanfacine with a common SD of 15 mm Hg.

Analyses were done on an intention-to-treat basis. Primary and secondary end point analyses were performed according to a preestablished statistical analysis plan. A fixed sequence approach was used to control the type 1 error rate for all of the prespecified primary and secondary end points (ie, if a comparison tested in the order specified failed to meet criteria for statistical significance, all of the subsequent comparisons were declared "not statistically significant"). ANCOVA was used to analyze the coprimary end points. Baseline comorbidity status and race (stratification factors for randomization), treatment group, and baseline value were variables in the model. Change in SBP or DBP from baseline to week 14 (or last observation carried forward up to study day 98 if week 14 value was missing) were the outcome variables in this model. Pairwise comparisons were made between treatment groups. Nominal P values are presented; however, the fixed sequence approach determined statistical significance of efficacy comparisons, as described above.

In addition, a post hoc analysis of time-weighted average change from baseline to week 14 in SBP and DBP was performed. The trapezoidal rule was used to calculate the area between the first postbaseline measurement and week 14 (or last available value up to study day 98 if week 14 was not collected) and then divided by the time interval over which it was collected. This value minus the baseline BP value resulted in time-weighted average change from baseline to week 14. Pairwise comparisons were again tested using an ANCOVA model with baseline value, race, comorbidity status, and treatment group included in the model.

The secondary end points of change from baseline to week 14 in mean 24-hour ambulatory BP data and estimated glomerular filtration rate were analyzed analogously to the coprimary end points. For the prespecified secondary end point of change from baseline in mean 24-hour BP, only ambulatory BP records that met predefined quality control criteria were used. A post hoc analysis including all of the available ambulatory records was also performed. The proportion of patients achieving SBP goal was tested using logistic regression with baseline SBP, treatment group, comorbidity status, and race included in the model. Laboratory and safety data were summarized as available with no imputation.

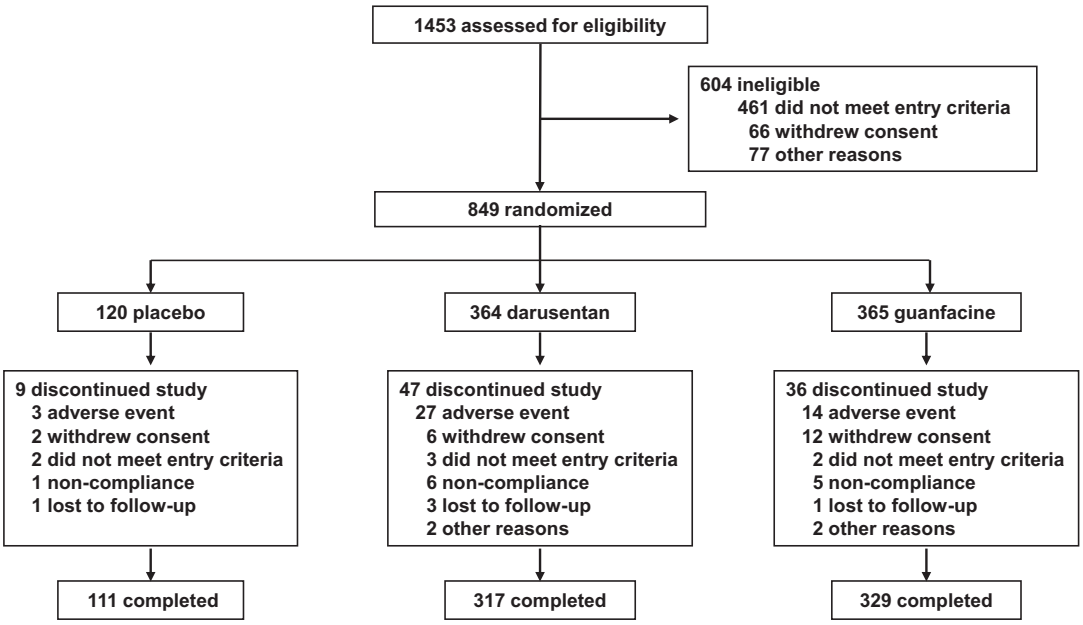

Figure 1. Trial profile. Patients who discontinued study participation before the primary end point assessments at week 14 are summarized. A total of 734 patients (86%) completed the study to week 14 on study drug. All 849 randomized subjects were included in the primary analyses (intent to treat). Ninety-two randomized patients withdrew from the study before the primary end point assessments at week 14 (44 for adverse events).

Results

Figure 1 shows the recruitment/participant disposition. Of the 1453 patients screened for this study, 849 were randomized, and 757 patients (89.2%) completed the study through week 14. All of the 849 randomized patients were included in the primary analyses (intention to treat).

Baseline characteristics were similar across the 3 treatment groups (Table 1). Consistent with entry criteria, all of the patients were receiving a diuretic at baseline (Table 1). Thiazide-type diuretics were given to 806 patients (95%), 688 (85%) of whom were taking hydrochlorothiazide (median dose: 25.0 mg/d; range: 6.3 to 100.0 mg/d), and 58 patients

Table 1. Baseline Patient Characteristics

Characteristic	Placebo (N=120)	Darusentan (N=364)	Guanfacine (N=365)	All Patients (N=849)
Age, y	63±9	62±9	62±9	62±9
Women, n (%)	49 (41)	168 (46)	161 (44)	378 (45)
Black, n (%)	11 (9)	36 (10)	40 (11)	87 (10)
Body mass index, kg/m^2	31±5	32±5	32±5	32±5
eGFR, mL/min per 1.73 m^2	77±20	82±22	80±23	80±22
History of heart disease, n (%)	24 (20)	77 (21)	92 (25)	193 (23)
Type 2 diabetes mellitus, n (%)	49 (41)	150 (41)	151 (41)	350 (41)
Chronic kidney disease, n (%)	29 (24)	80 (22)	99 (27)	208 (24)
Albuminuria, n (%)*	36 (30)	96 (26)	105 (29)	237 (28)
≥4 antihypertensive drugs, n (%)	43 (36)	130 (36)	138 (38)	311 (37)
Diuretic drugs, n (%)	120 (100)	364 (100)	365 (100)	849 (100)
RAS inhibitors, n (%)	115 (96)	349 (96)	352 (96)	816 (96)
Calcium-channel blockers, n (%)	75 (63)	241 (66)	253 (69)	569 (67)
β-blockers, n (%)	70 (58)	226 (62)	221 (61)	517 (61)
SBP, mm Hg	152±11	151±11	152±11	152±11
DBP, mm Hg	89±10	88±10	87±10	88±10
Heart rate, bpm	69±10	68±10	69±10	69±10
24-h SBP, mm Hg†	134±14	134±15	134±14	134±14
24-h DBP, mm Hg†	80±11	78±11	77±11	78±11

Data are mean±SD unless otherwise noted. eGFR indicates estimated glomerular filtration rate; RAS, renin angiotensin system.

*Albuminuria was defined as urinary albumin-to-creatinine ratio at ≥30 mg of albumin per gram of creatinine at baseline.

†Data include all of the patients with ABPM records that met prespecified quality control criteria at baseline.

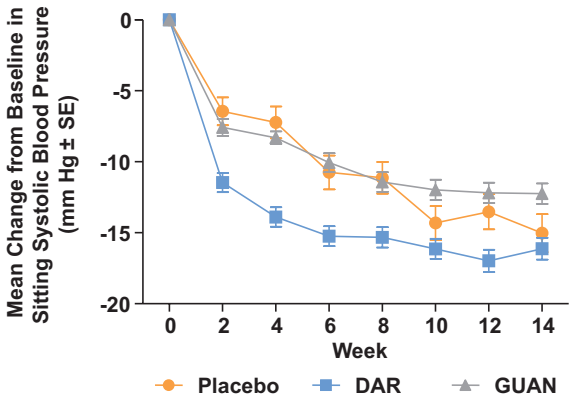

Figure 2. Mean change from baseline in sitting systolic BP over time. Observed values at each time point are displayed.

(7%) were on a loop diuretic. In addition, 536 patients (63%) were receiving exactly 3 full-dose antihypertensive drugs at baseline, and 311 (37%) were taking ≥4 agents. Approximately 296 patients (35%) were on a statin, 298 (35%) on aspirin, and 295 (35%) were receiving ≥1 antidiabetic drug (including insulin). The maximum dose of darusentan received during the study was 50 mg/d for 108 patients (30% of patients randomized to darusentan), 100 mg/d for 85 patients (23%), and 300 mg/d for 171 patients (47%).

At the predetermined end point of 14 weeks, the mean decrease in sitting SBP was 14±14 mm Hg for the placebo group, 15±14 mm Hg for the darusentan group, and 12±13 mm Hg for the guanfacine group. No significant difference was observed between darusentan and placebo treatment for change from baseline in SBP (the first comparison in the fixed-sequence multiple comparison procedure). Patients receiving darusentan had greater decreases in SBP (15±14 mm Hg) and DBP (10±0.5 mm Hg) after 14 weeks when compared with guanfacine (12±13 mm Hg and 6±0.4 mm Hg; $P<0.001$ for both comparisons), whereas patients on placebo experienced a larger decrease in DBP (8±0.8 mm Hg) as compared with guanfacine ($P=0.010$). Because of the unexpected placebo response that was observed over time in this study, particularly after week 8 (Figure 2), a post hoc analysis of time-weighted average change from baseline for clinic SBP and DBP was also performed (Figure 3). Compared with placebo or guanfacine, darusentan treatment resulted in greater reductions in both SBP and DBP ($P<0.001$ for all comparisons; Figure 3).

Based on mean sitting clinic BPs recorded at week 14, SBP goal (<130 mm Hg if the patient had DM or CKD; <140 mm Hg for all others) was achieved by 53 patients (44%) in the placebo group, 174 (48%) on darusentan, and 127 (35%) in the guanfacine group ($P=0.049$ placebo versus guanfacine; $P<0.001$ darusentan versus guanfacine). Differences between darusentan and placebo were not significant.

Changes from baseline in 24-hour ambulatory BP for all 3 of the treatment groups are displayed in Figure 4. This analysis included 668 randomized patients (79%) who had ambulatory BP monitoring at baseline and at week 14. Patients receiving darusentan had greater reductions in mean 24-hour SBP and DBP than either the placebo or the guanfacine groups (Figure 4). The baseline (all patients pooled) and end-of-study ambulatory values by treatment group and clock hour for mean SBP over the 24-hour recording period are shown in Figure 5. Nearly identical results were observed for these end points when analyzed according to the prespecified analysis, including only patients who had ambulatory records at baseline and at week 14 that met predefined quality control criteria (n=353 [42%]; data not shown).

During the trial, diuretic therapy could be intensified at the discretion of the investigators to manage fluid retention (apart from within 2 weeks of the primary end point assessment at week 14). Five patients (4%) in the placebo group, 47 (13%) in darusentan group, and 23 (6%) in the guanfacine group had diuretic agents added (or altered to increased doses) by investigators to treat fluid-related adverse events. Because of the potential effect of these diuretic changes on the primary efficacy results, mean changes in SBP and DBP were also evaluated, including only the last available BPs before implementation of the changes to diuretic drugs. The results of this analysis (data not shown) were similar to the prespecified primary end point data described earlier in this section.

Although changes to concomitant antihypertensive therapy were not allowed during the treatment period, a small number of patients did have adjustments to background medications during

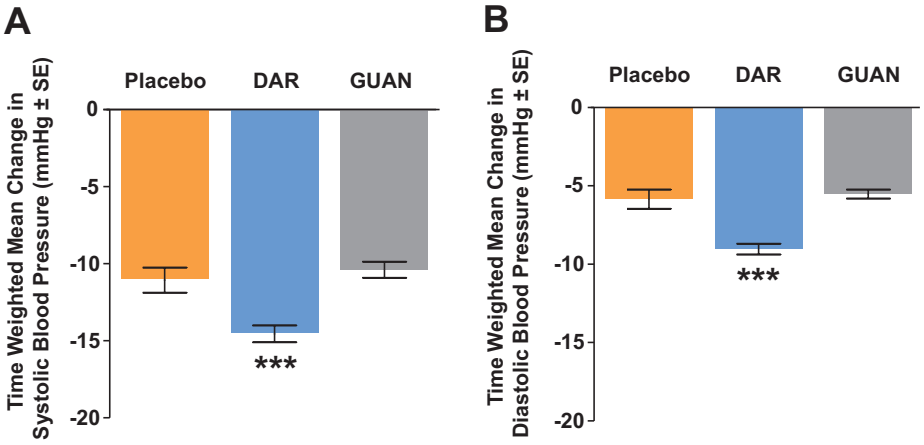

Figure 3. Time-weighted average change in BP from baseline to week 14 (based on time course in Figure 2). All of the randomized patients were included in this analysis. ***$P<0.001$ as compared with placebo or guanfacine.

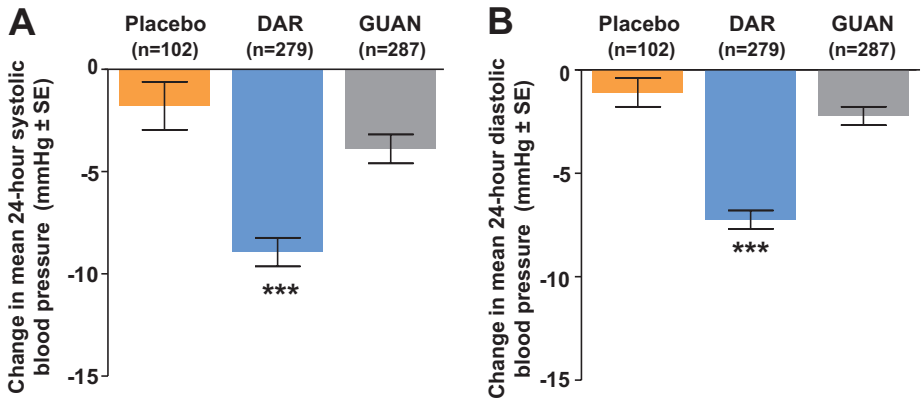

Figure 4. Mean changes from baseline in 24-hour ambulatory BP after 14 weeks. Only patients with both baseline and week 14 ambulatory readings were included in this analysis. ***$P<0.001$ as compared with placebo or guanfacine.

the trial, 4 patients (3%) in the placebo group, 16 (4%) in the darusentan group, and 11 (3%) in the guanfacine group. Given the even distribution across the treatment groups and the small number of individuals in whom these changes were made, it is unlikely that such occurrences affected the primary efficacy results.

Table 2 shows the most frequently reported adverse events during the study. The primary adverse effects observed in the darusentan group were edema and/or fluid retention. Most reports of edema or other signs of fluid retention during the study occurred during the first 6 weeks after start of treatment. Overall, 15 patients (4%) in the darusentan treatment group versus no patients in the placebo group and 3 (1%) in the guanfacine group discontinued study participation or study drug because of fluid retention or peripheral edema. Two patients experienced events of cardiac failure in the study, 1 on darusentan and 1 on guanfacine. Similar to previous studies, blood hemoglobin concentrations were reduced in all of the groups but to a greater degree in patients receiving darusentan (0.9 g/dL in the darusentan group versus 0.2 g/dL on placebo and 0.1 g/dL on guanfacine). Blood cell counts and total bilirubin concentrations were unchanged (data not shown), suggesting an absence of hemolysis.

Serious adverse events are summarized in Table 2. There were 3 deaths during the study, 1 in the placebo group (sudden cardiac death) and 2 in the darusentan group (arrhythmia and c-antineutrophilic cytoplasmic antibodies-positive pulmonary renal syndrome). None of the causes of death were considered related to study drug by the site investigators.

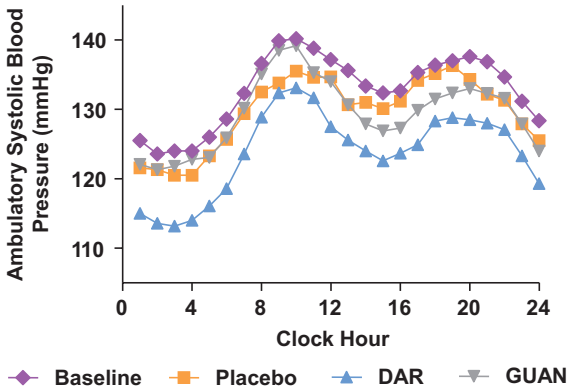

Figure 5. Ambulatory systolic BP over 24 hours. Patients with ambulatory BP readings at baseline and end of study were included in this summary. At baseline, all of the treatment groups were combined. Results at end of study are displayed by clock hour and randomized treatment group.

Discussion

In contrast to our first pivotal trial of darusentan in RHTN,[11] darusentan failed to show superiority over placebo for change

Table 2. Summary of Adverse Events

Treatment-Emergent Adverse Events, n (%)	Placebo (N=120)	Darusentan (N=364)	Guanfacine (N=365)
Any AE	71 (59)	266 (73)	213 (58)
Fluid retention and/or edema	14 (12)	101 (28)	44 (12)
Headache	4 (3)	24 (7)	15 (4)
Dizziness	3 (3)	16 (4)	14 (4)
Weight increased	3 (3)	12 (3)	7 (2)
Anemia	0 (0)	11 (3)	1 (<1)
Upper respiratory tract infection	1 (1)	11 (3)	7 (2)
Back pain	2 (2)	12 (3)	5 (1)
Fatigue	2 (2)	6 (2)	12 (3)
Dry mouth	1 (1)	7 (2)	32 (9)
Any serious AE	6 (5)	23 (6)	9 (3)
Deaths	1 (1)	2 (1)	0 (0)
Cardiac-related serious AE*	0 (0)	4 (1)	2 (<1)
Hypersensitivity/allergy-related serious AE†	0 (0)	5 (1)	0 (0)
Liver function test abnormality‡	0 (0)	8 (2)	3 (1)
Any AE leading to study drug discontinuation	3 (3)	44 (12)	21 (6)

*Events by patient were arrhythmia, myocardial infarction/cardiac failure, myocardial ischemia, and sinus arrest in the darusentan group, as well as atrial fibrillation/cardiac failure and second degree atrioventricular block in the guanfacine group.

†Events were 2 facial edema and 1 angioedema (none of which required hospitalization), 1 leukocytoclastic vasculitis, and 1 fatal c-antineutrophilic cytoplasmic antibodies–positive pulmonary-renal syndrome.

‡Any elevation >3 times the upper limit of normal in amino- or aspartate-aminotransferases was required to be reported as a serious adverse event in the study, according to the protocol. None of these events required hospitalization, and all resolved on discontinuation of study drug.

from baseline to week 14 in clinic SBP, and all of the subsequent prespecified efficacy end points (multiple comparison procedure) were not statistically significant. The inability to show a difference at week 14 in SBP was primarily because of an unexplained large placebo response (−14/−8 mm Hg) late in the trial. Clinically significant differences in clinic BPs in favor of darusentan were observed up to week 8 of the study. The SBP treatment response to darusentan was slightly less in this trial compared with the previous trial (−15 mm Hg as compared to −17 mm Hg in the earlier trial).[11] In the present study, darusentan demonstrated greater reductions in 24-hour ambulatory SBP and DBP over placebo.

The unusually large and relatively abrupt placebo effect on clinic BP after week 8 is puzzling. A number of possibilities could account for this larger-than-expected decrease in BP in the placebo group, including acute reductions in BP at specific study sites, unauthorized alterations in the number or dose of concomitant antihypertensive medications, per protocol adjustments adding or increasing the dose of diuretics, and study drug administration errors. All of these possibilities were investigated, and none provided an explanation for the observed results in the placebo group.

The reductions in mean 24-hour BP observed in the darusentan treatment group in this study (approximately −10/−8 mm Hg) were nearly identical to those seen in the previous pivotal trial.[11] If changes in ambulatory BP had been prospectively selected as the primary end point, the outcome of this study may have been viewed differently. To this point, it is also interesting to note the findings of the African American Study of Kidney Disease and Hypertension, a long-term outcome study that demonstrated no benefit on renal outcomes based on changes in office BPs.[13] However, this conclusion was proven incorrect when the ambulatory BPs showed that two thirds of the subjects with controlled clinic BPs had masked hypertension (ie, controlled office BP with elevated day or night ambulatory pressures).[14] Moreover, this trial showed lower rates of target organ damage among those who had BP control by both office measurements and ambulatory monitoring.[14] Hence, a lesson learned from the current trial is that future hypertension trials should seriously consider using change in ambulatory BP, rather than office BP, as the primary end point.

In the present study, we also compared darusentan with another active drug, guanfacine. The choice of this agent rests with the understanding that it has a distinctive pharmacological mechanism for BP reduction that theoretically should have potentiated the effects of the other medications.[15–17] Spironolactone was not selected because, when this study was designed, it was felt that the available data did not support the use of this drug for all of the patients with RHTN. Guanfacine at the dose used (1 mg) did not lower BP substantially in our trial. This was in contrast to placebo that reduced both clinic SBP and DBP from baseline to the end of the study. Interestingly, in previous trials in patients with essential hypertension, guanfacine at a dose of 1 mg/d was effective in lowering BP as compared with placebo.[18,19]

Although a strength of this trial was the inclusion of a well-characterized cohort of RHTN patients with multiple comorbidities, especially those with type 2 DM and CKD, it had important limitations. Using a time point–specific primary end point at week 14 for clinic BP instead of the change of BP over the entire duration of the trial did not use all of the BP data collected in the study. In addition, the inclusion criteria were limited to clinic BPs rather than ambulatory recordings. This could have resulted in a high rate of hypertensive patients with office resistance (ie, elevated BP only in the clinic) enrolled in the trial.

Consistent with previous darusentan trials, more patients discontinued the trial because of any adverse event in the darusentan group as compared with both placebo and guanfacine (darusentan 12%, placebo 3%, and guanfacine 6%). Although there were no differences in deaths among the groups, more adverse events were noted in the darusentan group primarily related to fluid overload and/or edema. This volume overload is also likely responsible for the potential hemodilution effect evidenced by a 0.9-g/dL reduction in hemoglobin in patients receiving darusentan.

BP goals are very difficult to attain in patients with RHTN, even after the addition of a fourth or fifth drug. Very few drugs when added to existing triple or quadruple therapy achieve a higher percentage of BP goals in such individuals. Selective endothelin A receptor antagonists, when used as ancillary agents, may have a role in helping patients achieve lower BPs when they are already taking 3 or 4 maximally dosed agents and still not at BP goal. In general, the ambulatory BP results from both well-constructed and powered pivotal trials suggest that darusentan is effective in lowering BP in RHTN.[11] Moreover, although its safety profile may preclude its use as initial antihypertensive therapy, it does not clearly mitigate its use in RHTN, except in people with HF or those with diseases, such as proteinuric kidney disease, where volume overload could lead to dire consequences.

Perspectives

BP goals are very difficult to achieve in people with RHTN even after the addition of a fourth or fifth drug. Very few agents have demonstrated efficacy as add-on therapy in this clinical situation. The results of the 24-hour ambulatory BP analysis of this trial, taken together with the primary results of earlier trials, suggest that selective ERAs may have a role in the treatment of RHTN and may help more patients achieve their BP goals. The concern about the use of this class of agents centers on volume retention and exacerbation of HF, an effect that occurs in spite of diuretic use. This volume expansion has been observed in all of the trials with darusentan and is a common adverse effect of other ERAs. Thus, the use of selective ERAs to facilitate BP control in patients with RHTN needs to be tempered with the caution that people with a history of HF or those who developed or are at significant risk of developing HF symptoms after volume excess should not use this class of agents. In addition, the long-term benefit-to-risk profile (including outcomes) for this class of agents in the treatment of RHTN has not been established. Lastly, the results of this trial clearly demonstrate the pitfall of arbitrarily selecting a specific end point in time for a BP outcome relative to assessing the total BP control over a

given study period. Moreover, this study highlights the importance of ABPM end points, as opposed to end points based on office BPs, in the design of hypertension studies.

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Disclosures

We were scientific advisors to Gilead Sciences, Inc, on this project. J.V.L., S.A., and P.S. are current or former employees of Gilead Sciences, Inc.

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