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Research Article

Long-term safety of nebivolol and valsartan combination therapy in patients with hypertension: an open-label, single-arm, multicenter study

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Abstract

Long–term safety of a free–tablet combination of nebivolol and valsartan was assessed in a Phase III, open–label trial (NCT01415505). Adults with hypertension entered a 4–week placebo run–in phase, followed by a 52–week treatment phase. Initial dosage (Neb/Val 5/160 mg/d) was titrated up to 20/320 mg/d to achieve blood pressure (BP) goal (JNC7 criteria), with the addition of hydrochlorothiazide (up to 25 mg/d) if needed. Safety and tolerability parameters included adverse events. Efficacy assessments included baseline–to–endpoint change in diastolic BP and systolic BP and the percentage of patients who achieved BP goal. All analyses were performed using descriptive statistics. Study completion rate was 60.4% (489/810). The most frequent reason for discontinuation was insufficient therapeutic response (8.4%). Adverse events were experienced by 59.2% of patients, with the most common being headache (5.7%), nasopharyngitis (5.0%), and upper respiratory tract infection (4.6%). Three (0.4%) deaths occurred during the study; none was considered related to study medication. Mean ± standard deviation changes from baseline at week 52 (observed cases) were −25.5 ± 15.9 mm Hg (systolic BP) and −19.0 ± 8.7 mm Hg (diastolic BP). A total of 75.7% nebivolol/valsartan–treated and 57.8% nebivolol/valsartan/hydrochlorothiazide–treated completers achieved BP goal. Long–term treatment with nebivolol and valsartan in adults with hypertension was safe and well–tolerated. J Am Soc Hypertens 2014;8(12):915–920. © 2014 American Society of Hypertension. All rights reserved.

Keywords: Angiotensin receptor blocker; beta-blocker; blood pressure; clinical trial.

Introduction

Over two–thirds of individuals with hypertension require more than one drug to achieve blood pressure (BP) control.[1,2] There is a dearth of data about combining β–blockers and renin–angiotensin–aldosterone system (RAAS) inhibitors, but it has been suggested that such combinations would be suboptimal, due to a partial overlap in the mechanism of action.[3]

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Nebivolol is a β_1–selective antagonist with nitric oxide–dependent vasodilatory properties[4] and has been approved for the treatment of hypertension, alone or in combination with other antihypertensive agents. The β_1:β_2 receptor affinity for nebivolol has been estimated at 321:1 for doses up to 10 mg/day, but the high β_1 selectivity may be lost at the highest approved, but clinically rarely used, dose of 40 mg/day.[5] Compared with atenolol, nebivolol has been shown to decrease central pulse pressure and the augmentation index,[6] although the two drugs lower brachial BP, pulse rate, and plasma renin activity to a similar extent.[7] Valsartan is an angiotensin II receptor blocker (ARB), and is already a component of several fixed–dose combinations.[8–10] The antihypertensive efficacy of valsartan and other ARBs is based on reduction of peripheral resistance[11] and, similar to other ARBs,[9] valsartan has been shown to reduce the levels of pro–inflammatory cytokines in patients with hypertension.[12] Both nebivolol and valsartan have an excellent safety and tolerability profile.[13–15]

Here we report the results of an open–label study that assessed the long–term safety of nebivolol and valsartan, administered as a free–tablet, flexible–dose combination, in adults with stage 1 or 2 hypertension (per JNC7 criteria[1]).

Methods

Ethical Conduct

This study was conducted in compliance with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines and the US Food and Drug Administration guidelines for good clinical practice; and in accordance with the ethical principles that originate from the Declaration of Helsinki and the US Food and Drug Administration Code of Federal Regulations Title 21, section 312.120. All enrolled patients provided voluntary, written informed consent and Health Insurance Portability and Accountability Act (HIPAA) authorization prior to participating in any study procedures. The institutional review boards of all participating centers approved the study protocol, informed consent form, and information sheet advertisements.

Study Design

This was a Phase III, multicenter, open–label, single–arm trial (NAC-MD-02; NCT01415505) conducted in the US. Following a 1–week screening, participants entered a 4–week single–blind placebo run–in phase, followed by a 52–week treatment period during which they received the free–tablet combination of nebivolol 5 mg/day and valsartan 160 mg/day. The initial dosage (Week 0) of 5/160 mg/day nebivolol/valsartan was doubled to 10/320 mg/day at Week 2, and it was further increased to 20/320 mg/day if patients did not achieve BP goal (SBP/DBP $\leq$140/90 mm Hg [without diabetes] or $\leq$130/80 mm Hg [with diabetes]) after at least 4 weeks of treatment at the 10/320 mg/d dosage. If BP goal was not met after a minimum of 10 weeks on the 20/320 mg/d dosage, 12.5 mg/d hydrochlorothiazide (HCTZ) was added and doubled 4 weeks thereafter to 25 mg/d if BP goal was still not achieved. Patients who did not achieve BP goal after 14 weeks of adding HCTZ to their regimen (starting with the 12.5 mg/d dosage) were discontinued from the study. After 52 weeks of treatment, all patients underwent 1 week of down–titrating their nebivolol dosage (20 mg to 10 mg to 5 mg to placebo, in 3–day increments, as applicable), before all study medication was discontinued.

Participants

Men and women ages 18 years or older were eligible to participate if they had a heart rate of $\geq$55 beats per minute (except for patients already on β-blockers), a normal physical examination at Screening, and stage 1 or 2 hypertension, with a recent DBP measurement of $\geq$90 mm Hg and $<$110 mm Hg if currently receiving hypertension treatment, DBP $\geq$95 mm Hg and $<$110 mm Hg at Screening if currently untreated or if previously diagnosed but untreated for at least 4 weeks prior to Screening. Individuals were enrolled in the treatment phase if during the run–in phase they demonstrated $\geq$80% and $\leq$120% adherence to single–blind placebo treatment and if their mean seated DBP measurements at the end of the run–in phase and at Week 0 (study enrollment visit) were $\geq$95 mm Hg and $<$110 mm Hg. Treatment–naïve patients and patients who were untreated for at least 4 weeks were eligible for early enrollment if SBP measured $\geq$180 mm Hg or DBP $\geq$110 mm Hg (“safety value”) and if a repeat measurement within 3 days was below the safety value, or if DBP measured $\geq$95 mm Hg and $<$110 mm Hg and SBP $<$180 mm Hg for at least two consecutive visits during the run–in phase. Major reasons for exclusion were secondary hypertension, severe hypertension (SBP $\geq$180 mm Hg or DBP $\geq$110 mm Hg), current treatment with four or more antihypertensive medications (including components of fixed–dose combinations), contraindication to discontinuing current antihypertensive treatment, upper arm circumference $>$42 cm, the presence of coronary artery disease requiring treatment with a β-blocker, calcium channel blocker, or chronic nitrates, reactive airway disease, chronic obstructive pulmonary disease, second- or third-degree heart block or sick sinus syndrome, clinically significant cardiovascular disease, event, or procedure within 6 months from Screening, heart failure, hypertensive retinopathy (Keith–Wagener grade III or IV), type 1 diabetes, poorly controlled type 2 diabetes (HbA_{1C} $\geq$8%), uncontrolled thyroid disease within 3 months of Screening, record of substance abuse within 2 years from Screening or a positive urine drug test at Screening, inflammatory bowel

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