Comparison of 26-Week Efficacy and Tolerability of Telmisartan and Atenolol, in Combination with Hydrochlorothiazide as Required, in the Treatment of Mild to Moderate Hypertension: A Randomized, Multicenter Study

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ABSTRACT

Objective: This study was undertaken to compare the efficacy and tolerability of telmisartan, a novel antihypertensive agent, and atenolol, a well-established beta-blocker, in the treatment of mild to moderate hypertension.

Methods: This 26-week, multicenter, randomized, double-blind, double-dummy, parallel-group, titration-to-response study compared doses of telmisartan (40 mg titrated to 80 mg titrated to 120 mg) with atenolol (50 mg titrated to 100 mg) required to achieve diastolic blood pressure (DBP) control (≤90 mm Hg or a decrease from baseline of ≥10 mm Hg). Open-label hydrochlorothiazide (HCTZ) 12.5 or 25 mg was added if needed according to a prespecified titration rule. Men and women aged ≥18 years with mild to moderate hypertension (morning mean supine DBP [SDBP] ≥95 mm Hg and ≤114 mm Hg) were eligible to participate. Patients with significant cardiovascular, metabolic, hepatic, or renal dysfunction or chronic obstructive pulmonary disease were excluded. The primary efficacy end point was trough SDBP response at 26 weeks; secondary efficacy end points included changes from baseline at trough in both standing and supine DBP and systolic blood pressure (SBP), and heart rate after 4, 8, 16, and 26 weeks; SBP control (reduction from baseline of ≥10 mm Hg); normalization of supine SDBP to ≤90 mm Hg; and the need for add-on HCTZ. Changes in quality of life were also examined. Adverse events were obtained from spontaneous reporting and recorded. Serious adverse events were reported to the sponsor according to predefined timelines.

*The study group members are listed in the Acknowledgments.

Accepted for publication October 11, 2000.
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Results: A total of 533 patients from 49 centers participated. Patients’ mean age was 57.9 years (range, 22–79 years); 55.9% (298/533) of the population was male and 98.1% (523/533) was white. Of the 533 patients randomly assigned to treatment and included in the safety analysis, 520 (97.6%) were included in the efficacy analysis; 346 received telmisartan and 174 received atenolol. A total of 489 patients (91.7%) completed the study (325 [93.9%], telmisartan; 164 [94.2%], atenolol). Full SDBP response (trough SDBP ≤90 mm Hg and/or a reduction from baseline of ≥10 mm Hg) was observed in 84% and 78% of telmisartan- and atenolol-treated patients, respectively; this difference was not statistically significant. Final SBP/DBP reductions of 20.9/14.4 mm Hg were observed for the telmisartan regimen versus 16.7/13.3 mm Hg for the atenolol regimen; only the difference in SBP was significant (P = 0.005). Reduction from baseline in SBP of ≥10 mm Hg was achieved by 80% of telmisartan-treated and 68% of atenolol-treated patients (P = 0.003). Adverse events were reported by 52.1% of patients given telmisartan and 61.2% of patients given atenolol; this difference was not statistically significant. Most events were mild or moderate. Although fatigue and male impotence were more common in atenolol-treated patients (3.4% and 4.0%, respectively), the incidence of these adverse events was too low to differentiate statistically.

Conclusions: Telmisartan appears to be at least as effective as atenolol in the treatment of mild to moderate hypertension and may be better tolerated.

Key words: telmisartan, angiotensin II antagonist, atenolol, hydrochlorothiazide, efficacy, tolerability. (Clin Ther. 2001;23: 108–123)

INTRODUCTION

Angiotensin II (All), the principal effector hormone in the renin-angiotensin-aldosterone system, activates several powerful physiologic responses that help regulate blood pressure, including systemic and renal vasoconstriction, sodium reabsorption by the renal proximal tubule, and stimulation of aldosterone and adrenergic hormone release by the adrenal glands.1 These actions are mediated principally via a specific All receptor subtype, AT1, which is located on the cell-wall surfaces of a variety of tissues including the heart, kidneys, and arteries.2

Telmisartan belongs to a new class of orally active and highly selective nonpeptide substituted benzimidazole AT1-receptor antagonists.3-5 Preclinical pharmacology studies have demonstrated that telmisartan specifically and potently inhibits the All receptor subtype AT1.5 Telmisartan does not affect other aspects of the renin-angiotensin-aldosterone system, such as angiotensin-converting enzyme (ACE) activity; nor does it interact with the AT2 receptor subtype or other receptor systems, including those for catecholamines, serotonin, histamine, or adenosine.5

Telmisartan has high bioavailability (40%–60%), a half-life of 24 hours, and a volume of distribution of 600 L/kg; binds tightly and specifically to AT1 receptors; and may have some inherent natriuretic activity.6-8 It has been shown in previous studies to be an extremely effective antihypertensive agent, producing high response rates compared with other commonly used agents.7-9 For example, in a 52-week, randomized, placebo-controlled, parallel-group study9 of telmisartan and the ACE inhibitor lisinopril, both drugs showed similarly high control rates; 67% of patients
given telmisartan and 63% of patients given lisinopril achieved diastolic blood pressure (DBP) control of <90 mm Hg. In addition, during a 12-week, double-blind trial, a 24-hour mean DBP of <85 mm Hg was achieved in 71% of telmisartan-treated patients and 55% of those treated with amlo- dipine. Telmisartan at both 40- and 80-mg doses has also been shown to result in significantly greater reductions over the 24-hour dosing interval in both DBP and systolic blood pressure (SBP) compared with losartan 50 mg (7.4/11.5 mm Hg with telmisartan 40 mg; 8.4/13.3 mm Hg with telmisartan 80 mg; 4.9/8.0 mm Hg with losartan 50 mg; P < 0.05). Furthermore, because it has a long duration of action (mean terminal half-life of 24 hours, the highest in its class) and high tissue penetration (illustrated by the highest volume of distribution in its class), telmisartan has a pharmacokinetic profile that differentiates it from other angiotensin-receptor blockers.

Long established as first-line therapy for the treatment of hypertension, beta-blockers have demonstrated their efficacy in accomplishing the primary goals of antihypertensive therapy—controlling blood pressure and reducing cardiovascular morbidity and mortality. The purpose of this 26-week, dose-titration study, performed in phase IIIa, was to compare the efficacy and tolerability of telmisartan tablets (40 mg titrated to 80 mg titrated to 120 mg) versus atenolol capsules (50 mg titrated to 100 mg) administered once daily, alone or with open-label hydrochlorothiazide (HCTZ) 12.5 or 25 mg. The study consisted of 3 periods: screening, placebo run-in, and double-blind. The study design was approved by ethics committees in each country (Germany, the Netherlands, and the United Kingdom) and performed in accordance with the Declaration of Helsinki (September 1989 revision).

**Study Design**

This 26-week, multicenter, randomized, double-blind, double-dummy, parallel-group, titration-to-response study compared the efficacy and tolerability of telmisartan tablets (40 mg titrated to 80 mg titrated to 120 mg) versus atenolol capsules (50 mg titrated to 100 mg) administered once daily, alone or with open-label hydrochlorothiazide (HCTZ) 12.5 or 25 mg. The study consisted of 3 periods: screening, placebo run-in, and double-blind. The study design was approved by ethics committees in each country (Germany, the Netherlands, and the United Kingdom) and performed in accordance with the Declaration of Helsinki (September 1989 revision).

**Screening**

A complete medical history was obtained and a comprehensive physical examination conducted, including a 12-lead electrocardiogram (ECG), routine laboratory tests, and a pregnancy test for premenopausal women (aged <60 years) who were not surgically sterile. Blood pressure was assessed in the arm according to the recommenda-