Pre-clinical studies suggest that combined blockade of ETA and AT1 receptors reduces end-organ injury to a greater extent than either receptor antagonist alone. Towards this end, dual ET\text/AngII receptor antagonists (DARAs) have been developed. The first DARA was reported by Bristol Myers Squibb in 2002 and was based on the observation that ETA antagonists shared the same biphenyl core as several AT1 receptor blockers. A series of these biphenylsulfonamides were reported in 2003 and 2004 and found to be orally active in several rat models of hypertension (AngII, DOCA and SHR). Subsequent synthesis of a 2'-substituted N-3-isoxazolyl biphenylsulfonamide led to a second generation DARA compound with improved pharmacokinetics and enhanced ETA and AT1 receptor potency (Ki of 0.8 nM and 9.3 nM for human AT1 and ETA receptors, respectively). Pharmacopeia acquired the license for the DARA, renaming it PS433540. Based on several Phase I studies, they conducted a single blind Phase Iia study in patients with mild to moderate hypertension (NCT00522925) with a primary endpoint of change in 24-hr systolic BP after 4 weeks of placebo (N = 28), 200 mg (N = 38) or 500 mg (N = 36) daily of drug. The results, reported in 2008, demonstrated no change with placebo, a 12/9 mm Hg or 15/10 mm Hg drop in SBP/DBP with 200 mg or 500 mg of drug, respectively. There were no significant adverse events. Ligand Pharmaceuticals acquire Pharmacopeia and conducted a Phase Iib trial in a similar group of hypertensive patients (NCT00635232). Patients were treated daily with 200 mg (N = 55), 400 mg (N = 48) or 800 mg (N = 20) PS433540, placebo (N = 39), or 300 mg irbesartan (N = 44). The primary endpoint was change in office SBP after 12 weeks. The SBP/DBP decreased by 1.8/0.2, 10.7/7.1, 13.2/7.2, 14.2/9.2 and 23.4/14.3 in the placebo, irbesartan, 200, 400 and 800 mg PS433540 groups, respectively. Peripheral edema (all mild to moderate) was noted in 2–3% of patients treated with irbesartan, placebo or 200 mg PS433540, while it occurred in 6.9 and 10.7% of patients receiving 400 and 800 mg PS433540, respectively. More patients on the highest DARA dose had dizziness, flushing and GI symptoms. Ligand licensed the DARA to Retrophin in 2012 who are currently planning a Phase II clinical trial (NCT01613118) with 4 different doses of the now renamed RE-021, as well as the active comparator irbesartan, in 72 patients, aged 8–50 years, with focal segmental glomerulosclerosis. The primary outcome will be a reduction in albumin excretion rate after 6 weeks of treatment. Finally, another DARA has been developed by Torrent Pharmaceuticals, termed TRC120038, a modified biphenylsulfonamide, with an in vitro EC50 of 3 nM and 158 nM for human AT1 and ETA receptors, respectively. Studies in ob-ZSF1 rats showed a greater reduction in mean BP with TRC120038 than with candesartan, as well as reduced renal dysfunction and improved cardiac function. In summary, DARAs are in the early phases of study. Preclinical trials and early clinical trials suggest that this new class of drugs may be well tolerated and could be efficacious in treating cardio-renal diseases where targeting both ETA and AT1 would likely be beneficial.

Good and bad news about single and dual biphenyl endothelin ETA and angiotensin AT1 receptor antagonists

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Background: AT1 antagonists like irbesartan and valsartan (IRB, VAL) and an ETA antagonist like BMS-193884 (BMS) share a core biphenyl structure. We tested the hypothesis that hybrids of these compounds act as dual ETA/AT1 receptor antagonists (DARA).

Methods: We compared effects of IRB, VAL and BMS with those of structural chimeras of IRB and BMS (PS-433540, DARA1) and of VAL and BMS (ACT-214145, DARA2), all synthesized at Actelion (CH). Contractile responses to angiotensin II (AngII) and endothelins (ET-1 and ET-2) were investigated in isolated rat mesenteric resistance arteries where ETB-agonists and -antagonists have no effects.

Results: Presence of IRB, VAL, DARA1 and DARA2 reduced the sensitivity and maximal responses to AngII-induced contraction with comparable apparent affinity (pA\textsubscript{2}: 9.5, 9.3, 9.7 and 9.2) while 10 nM BMS was not effective. Presence of IRB (\( \leq 3\text{ nM} \)) or VAL (\( \leq 100\text{ nM} \)) did not modify responses to ET-1 (1–16 nM). BMS (1–30 nM), on the other hand, potently reduced the sensitivity to ET-1 and ET-2 to the same extent (pA\textsubscript{2}: 9.2 and 9.2). Notably, this effect of BMS displayed saturability. It did not increase with increasing concentration in the supra-nanomolar range and this was more marked against ET-1 than against ET-2. The antagonistic effect of 10 nM BMS was significantly additive with that of the butenolide ETA-antagonist PD156707 (100 nM) but not of the cyclic pentapeptide ETA-antagonist BQ123 (1 \mu M). Furthermore, relaxing effects of 10 nM BMS on contractions induced by 16 nM ET-1 or ET-2 (\( \pm 57 \pm 11 \) and \( \pm 96 \pm 3 \)) were significantly larger than those predicted by the effect of BMS on the sensitivity to the peptides (\( \pm 20 \pm 10 \) and \( \pm 19 \pm 7 \)). These relaxing effects faded rapidly upon washout of both the agonist and antagonist. Finally and in sharp contrast to reported findings on radioligand–receptor binding and on pressor responses induced by big ET-1 in vivo, both DARA1 and DARA2 were \( > 2.5\text{ Log units} \) less effective in reducing rat mesenteric artery sensitivity to ET-1 and ET-2 than their common BMS core structure (pA\textsubscript{2}: 6.4, 6.2 and 9.2 against ET-1 and 6.8, 6.2 and 9.2 against ET-2).

Conclusion: The good news is that the biphenyl sulfonamide BMS is a negative allosteric modulator of arterial smooth muscle ETA receptors which unlike BQ123 and PD156707 acts most effectively on agonist-occupied activated receptors. The bad news is that the structure cannot be expended with an AT1-receptor antagonistic part without profound loss of affinity for ETA at the tissue level. Also, the results suggest that several allosteric modulatory sites may be present on ETA receptors.

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