British and Irish Hypertension Society
Committed to preventing cardiovascular disease

DRUG CLASSES

DIRECT RENIN INHIBITORS (DRI)

This is a new class of drugs, of which aliskiren, is the only one so far licensed for the treatment of hypertension.

Mechanism of action

Aliskiren was designed as an analogue of the natural substrate of renin: angiotensinogen. Aliskiren competes with angiotensinogen for access to the active site of the renin enzyme. The drug reduces plasma renin activity by about 75% and causes a sustained reduction in levels of angiotensin I and II.

Pharmacokinetics

All DRIs developed to date have had very low bioavailability – for aliskiren the figure is 2.7%. The early DRIs failed to achieve plasma concentrations sufficient to achieve worthwhile blood pressure reduction. Aliskiren's high affinity for the renin enzyme offsets the low bioavailability, with <1nmol/L required to achieve 50% inhibition of renin activity. Aliskiren is scarcely metabolised and has a long half-life of about 40 hours.

Clinical Studies

Aliskiren underwent phase 3 testing in some 15,000 patients and has also now been studied in three surrogate outcome trials. It is as effective at reducing blood pressure as representative drugs from each of the A,C,D classes; this has been demonstrated at steps 1 and 2 of the A/CD algorithm (i.e. as monotherapy, or as additional therapy). As a blocker of the renin-angiotensin system (RAS), and as predicted by the A/CD rule, aliskiren is more effective added to C or D than to ACEi or ARB. However there was about 4/2 mmHg additional fall in blood pressure when aliskiren was added to valsartan; and the addition of aliskiren to losartan reduced proteinuria in the 'AVOID' study of patients with diabetes.

Adverse events

At the licensed doses of 150 mg and 300 mg daily, there have been no adverse events in excess of placebo rates in clinical trials to date. Higher doses can cause diarrhoea. The same

precautions regarding electrolytes and renal function hold as for other RAS blockers. However, in the ALOFT study of patients with hypertension and heart failure, there was no excess of renal impairment or hyperkalaemia in patients receiving aliskiren in addition to other RAS blockers and spironolactone.

Indications and contra-indications

The BNF lists hypertension and pregnancy, respectively. NICE is not expected to have a view before scheduled revision of the NICE/BHS guidance, by when outcome data for aliskiren is due from the ALTITUDE study of patients with hypertension and diabetes. Meanwhile aliskiren is unlikely to be used in the UK in the early steps of the A/CD rule, since existing alternatives are either cheaper and/or have long-term outcome data of efficacy. DRI is an additional option for the treatment of patients not responsive to – or intolerant of – combinations of A+C+D. There are no randomised comparisons of existing drugs in such patients, and NICE/BHS recommends 'further diuretic, α-blockade or β-blockade'. These three options are now being compared in the BHS's 'PATHWAY' study funded by the BHF. On theoretical grounds, DRI might be considered an alternative to β-blockade, since both classes target the rate-limiting step of RAS, and are therefore the only drugs to reduce renin activity. In some patients with resistant hypertension, renin activity is already suppressed by salt retention; these patients benefit from an escalation of diuretic therapy. In patients receiving optimal diuretic therapy, or known to have high plasma renin, escalation of RAS blockade is the logical next option.

Future developments

Further DRIs are currently in phase 2 trials. The long-term benefits of aliskiren are being studied in a number of outcome trials, including heart failure and hypertension in the elderly. ACCELERATE is a shorter-term study which we mention because it started as a BHS initiative. The study is testing our hypothesis that compensatory haemodynamic responses to the initial drug for hypertension prevent blood pressure control from ever catching-up with the blood pressure achieved if combination treatment is employed from the start. The drugs in ACCELERATE are aliskiren and amlodipine, and the study will determine whether patients randomised to the combination for initial therapy have a lower blood pressure after 32 weeks than patients who are treated with aliskiren or amlodipine alone for the first 16 weeks.

References:

Brown MJ. Aliskiren. **Circulation**. **2008**;118:773-784

Brown MJ. Renin: friend or foe? **Heart 2007**;93:1026-1033