Shared care guideline

Aliskiren for resistant hypertension

Executive summary

- This shared care guideline outlines the responsibility of primary and secondary care clinicians in managing resistant hypertension with aliskiren.
- Clinical response can usually be expected in two weeks.
- The drug should be stopped if there is no improvement in blood pressure after three months therapy on 300mg daily or if the drug is not tolerated due to side-effects.

Sharing of care depends on communication between the specialist, GP and the patient or their parent/carer. The intention to share care should be explained to the patient and accepted by them. Patients are under regular follow-up and this provides an opportunity to discuss drug therapy. The doctor/healthcare professional who prescribes the medication has the clinical responsibility for the drug and the consequences of its use. Further information about the general responsibilities of the hospital specialist and GP can be found on the NHS Cambridgeshire and Peterborough CCG website.

1. Scope

Prescribing and monitoring by general practitioners after hospital initiation. General practitioners (GPs) may be asked to take over prescribing from secondary care if after three months the patient has shown a reduction in systolic blood pressure of >10mmHg.

2. Aim

To provide advice on safe prescribing and monitoring of aliskiren for use in adults with resistant hypertension with aliskiren.

3. Introduction

Aliskiren is a first in class direct renin inhibitor used for the management of hypertension. Aliskiren is licensed for the treatment of essential hypertension.

Aliskiren is restricted to patients with uncontrolled hypertension who have a greater than threefold elevation of plasma renin and are either intolerant of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers, or are already receiving more than three anti-hypertensive drugs (i.e. a subgroup of patients at stage 4 in the BHS guidelines) and only after consideration of alpha-adrenoceptor blocking drugs, potassium sparing diuretics and aldosterone antagonists.

In light of results from the ALTITUDE study, and subsequent Medicines and Healthcare Products Regulatory Agency (MHRA) advice, combining different agents from the RAAS is contraindicated in diabetic patients and in those with impaired renal function (GFR<60ml/min per 1.73m^2) owing to the risk of hyperkalaemia, changes in renal function and hypotension/syncope. Combining multiple medications targeting RAAS in other patients groups is not recommended, unless under specialist supervision and with close monitoring of electrolytes and renal function.

The ALOFT study previously demonstrated a positive effect of aliskiren on neurohumoral dynamics in patients with heart failure. Patients on an ACE/ARB plus beta blocker were randomised to either the addition of a placebo or aliskiren to their regime for 3 months. The

aliskiren group had a reduction in their plasma brain natriuretic peptide concentration compared to the placebo group in which plasma brain natriuretic peptide concentration increased. However the larger recent ATMOSPHERE study has shown that addition of aliskiren to an ACE inhibitor increases adverse effects, but does not actually improve outcomes (rate of death from cardiovascular causes or hospitalisation for heart failure) in patients with chronic heart failure and reduced ejection fraction.

4. Abbreviations

ACE	angiotensin-converting enzyme
ARB	angiotensin receptor blocker
BHS	British Hypertension Society
BNF	British National Formulary
BP	Blood pressure
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
GP	General Practitioner
MHRA	Medicines and Healthcare products Regulatory Agency
NYHA	New York Heart Association
NSAID	non-steroidal anti-inflammatory drug
P-gp	P-glycoprotein
RAAS	Renin-angiotensin system
SPC	Summary of product characteristics
U&E	Urea and Electrolytes

5. Dose and administration

The initial oral dose is:

- 150mg once daily for two months
- increasing to 300mg once daily after two months, if blood pressure (BP) response not adequate (i.e. improvement of systolic BP less than 10mmHg).

Clinical response can usually be expected in two weeks.

The drug should be stopped if there is no improvement in blood pressure after three months therapy on 300mg daily or if the drug is not tolerated due to side-effects.

Definition of adequate BP response
An acceptable response is classified as improvement of systolic BP of >5mmHg if another antihypertensive has been stopped when starting aliskiren or >10mmHg if aliskiren is used as add on therapy.

6. Adverse effects

Very common	(≥ 1 in 10)
Common	(≥ 1 in 100 and < 1 in 10)
Uncommon	(≥ 1 in 1000 and < 1 in 100)
Rare	(≥ 1 in 10000 and < 1 in 1000)

The most common side effect of aliskiren is diarrhoea. In the event of severe and persistent diarrhoea, aliskiren therapy should be stopped.

Other common side-effects are dizziness, arthralgia and hyperkalaemia.

Uncommon side effects include reports of acute renal failure in patients with risk factors for renal dysfunction (including hypervolemia, liver disease or kidney disease). There is also a risk of deterioration of renal function in patients with renal artery stenosis treated with aliskiren. Other uncommon side-effects include hypotension, palpitations, cough, pruritus, rash, other severe cutaneous reactions, increases in liver enzymes and peripheral oedema.

A rare side-effect of aliskiren is angioedema (a serious allergic reaction that causes swelling of the face or throat and occasionally other areas such as the hands). If angioedema occurs, patients should be advised to stop aliskiren and seek medical advice straight away.

Further information can be found in the BNF and in the SPC:
http://www.medicines.org.uk/emc/medicine/20049

See also MHRA drug safety update March 2012
http://www.mhra.gov.uk/home/groups/dsu/documents/publication/con146571.pdf
and June 2014 https://www.gov.uk/drug-safety-update/combination-use-of-medicines-from-different-classes-of-renin-angiotensin-system-blocking-agents-risk-of-hyperkalaemia-hypotension-and-impaired-renal-function-new-warnings

7. Contraindications

As monotherapy or in combination, in patients with an estimated glomerular filtration rate (eGFR) <30 mL/min per 1.73m^2.

Concomitant treatment with an ACE inhibitor or angiotensin II receptor antagonist in patients with diabetes mellitus (type 1 or 2) and eGFR <60 mL/min per 1.73m^2.

History of angioedema with previous dose/course of aliskiren.

Hereditary or idiopathic angioedema.

Hypersensitivity to the active substance or to any of the excipients.

All trimesters of pregnancy and in those planning on becoming pregnant. Aliskiren should also be avoided during breastfeeding.

The concomitant use of aliskiren with ciclosporin or itraconazole as these are highly potent P-gp inhibitors, and other potent P-gp inhibitors (quinidine, verapamil), is contraindicated.

Further information can be found in the BNF and in the SPC:
http://www.medicines.org.uk/emc/medicine/20049

8. Cautions

- Dual blockade of the RAAS by combining aliskiren with an ACE inhibitor or an angiotensin II receptor antagonist is not recommended. If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure.
- In the event of severe or persistent diarrhoea aliskiren should be stopped
- Due to the risk of hypotension with the first dose caution is advisable with concomitant use of:
    - potassium-sparing diuretics
    - potassium supplements
    - salt substitutes containing potassium
    - other substances that may increase serum potassium levels (e.g. heparin)

- Aliskiren should be used with caution in patients with serious congestive heart failure (NYHA functional class III-IV).
- In patients with marked volume- and/ or salt-depletion (e.g. those receiving high doses of diuretics), symptomatic hypotension could occur after initiation of treatment with aliskiren.
- Caution is needed when aliskiren is given in the presence of conditions pre-disposing to kidney dysfunction such as hypovolaemia, heart, liver or kidney disease, diabetes mellitus. Acute renal failure has been reported in at-risk patients receiving aliskiren. If renal failure occurs, treatment should be discontinued.
- There is an increased risk of renal insufficiency, including acute renal failure, when patients with renal artery stenosis are treated with aliskiren. If renal failure occurs, treatment should be discontinued.
- Caution is needed when aliskiren is administered with moderate P-gp inhibitors such as:
    - ketoconazole
    - itraconazole
    - clarithromycin
    - telithromycin
    - erythromycin
    - amiodarone
- Further information can be found in the BNF and in the SPC: http://www.medicines.org.uk/emc/medicine/20049

See also MHRA Drug Safety Update (March 2012) https://www.gov.uk/drug-safety-update/aliskiren-rasilez-risk-of-cardiovascular-and-renal-adverse-reactions and (June 2014) https://www.gov.uk/drug-safety-update/combination-use-of-medicines-from-different-classes-of-renin-angiotensin-system-blocking-agents-risk-of-hyperkalaemia-hypotension-and-impaired-renal-function-new-warnings

9. Interactions

Notable drug interactions (refer to BNF and SPC) include:

- Dual blockade of the RAAS with aliskiren, ARBs or ACE Inhibitor is associated with higher adverse events such as hyperkalaemia, reduced renal function and hypotension and with angioedema or angioedema-like reactions. Avoid concomitant use.
- Avoid concomitant use with potent P-gp inhibitors such as ciclosporin or itraconazole.
- Avoid fruit juices, herbal teas and any drinks containing plant extracts in patients on aliskiren due to the risk of therapeutic failure.
- P-gp is a major determinant of aliskiren bioavailability. Inducers of P-gp (St John's Wort, rifampicin) might therefore decrease the bioavailability of aliskiren.
- Caution is needed when aliskiren is administered with moderate P-gp inhibitors including:
    - ketoconazole
    - clarithromycin
    - telithromycin
    - erythromycin
    - verapamil
    - amiodarone
- NSAIDs may reduce the anti-hypertensive effect of aliskiren. In patients with compromised renal function (e.g. dehydrated patients or elderly patients), aliskiren given concomitantly with NSAIDs may result in further deterioration of renal function, including possible acute renal failure.

- Caution is advisable with concomitant use of:
  - potassium-sparing diuretics
  - potassium supplements
  - salt substitutes containing potassium
  - other substances that may increase serum potassium levels (e.g. heparin)
- The effect of furosemide may be reduced by concomitant use of aliskiren.
- Meals with a high fat content reduce absorption of aliskiren
- Further information can be found in the BNF and also in the SPC: http://www.medicines.org.uk/emc/medicine/20049

See also MHRA Drug Safety Update (March 2012) https://www.gov.uk/drug-safety-update/aliskiren-rasilez-risk-of-cardiovascular-and-renal-adverse-reactions and (June 2014) https://www.gov.uk/drug-safety-update/combination-use-of-medicines-from-different-classes-of-renin-angiotensin-system-blocking-agents-risk-of-hyperkalaemia-hypotension-and-impaired-renal-function-new-warnings

10. Monitoring standards and actions to take in the event of abnormal test results/ symptoms

Pre-treatment monitoring – in the hospital	
Renin, U&Es, eGFR	Within the two months prior to starting treatment with aliskiren
Monitoring during initial therapy – in the hospital	
Renin, U&Es, eGFR	Checked at 2-4 weeks after starting therapy. Then every three months if any abnormality of renal function or six-monthly if renal function is stable.
Monitoring during GP therapy	
U&Es, eGFR	Every three months if any abnormality of renal function or six-monthly if renal function is stable.
Blood glucose	Annual monitoring of blood glucose – fasting of possible – to exclude development of diabetes.

11. Actions to take in the event of abnormal test results/ symptoms

Abnormal blood test results	
Test	**Action**
U&Es, eGFR	Reduce dose to 150mg OD and discuss with specialist hospital clinician if eGFR falls by>10% on two successive measurements and/or plasma K^+ >5.5mol/l on two successive measurements.
Abnormal symptoms	
Diarrhoea	– Stop aliskiren if severe and persistent
Angioedema	– Stop aliskiren immediately and assess patient (may need hospital admission if swelling or ventilation compromised)
Patient ceases to benefit	
No improvement in blood pressure	– No improvement in blood pressure following 3 months treatment (<10mmHg improvement in systolic or <5mmHg if another drug stopped) – Refer to specialist hospital clinician

12. Shared care

Sharing of care assumes communication between the specialist, GP and the patient. The intention to share care should be explained to the patient and accepted by him/her. Patients are under regular follow-up and this provides an opportunity to discuss drug therapy.

The doctor who prescribes the medication has the clinical responsibility for the drug and the consequences of its use.

Shared care responsibilities

a. Consultant

- Assess benefits versus risks of aliskiren.
- To have excluded renal artery stenosis prior to drug commencement
- Initiate treatment and prescribe the first three months of treatment or until patient is stabilised (including up-titration from 150mg to 300mg at two months if required).
- Send a letter to the GP requesting shared care for this patient, outlining that benefits are considered to outweigh risks. Agreement to shared care cannot be assumed.
- Routine clinic follow-up on a regular basis (initially every 3-6 months until stable on therapy).
- Send a letter to the GP after each clinic attendance ensuring current dose, most recent blood results and frequency of monitoring are stated.
- Advise patients that they should stop aliskiren and seek medical advice straight away if they develop symptoms of angioedema, such as:
  - swelling of the face, eyes, lips or tongue (or both), hands and feet, or
  - difficulty breathing or swallowing
- Advise patients that aliskiren should not be taken if they have severe diarrhoea, vomiting (gastroenteritis) or they are dehydrated.
- Evaluation of any reported adverse effects by GP or patient.
- Advise GP on review, duration or discontinuation of treatment where necessary.
- Inform GP of patients who do not attend clinic appointments.
- Ensure that backup advice is available at all times.

b. General practitioner

- Monitor patient's overall health and wellbeing.
- Prescribe the drug treatment as described.
- Monitor blood pressure and blood results (U&Es, eGFR) in line with recommendations from hospital specialist.
- Refer to hospital specialist if eGFR falls by>10% on two successive measurements and/or plasma K+ >5.5mol/l on two successive measurements or if no improvement in blood pressure.
- Refer to hospital specialist when newly diagnosed glucose intolerance or diabetes.
- Be aware of interactions when starting new medications alongside aliskiren.

- Advise patients that they should stop aliskiren and seek medical advice straight away if they develop symptoms of angioedema, such as:
  - swelling of the face, eyes, lips or tongue (or both), hands and feet, or
  - difficulty breathing or swallowing.
- Advise patients that aliskiren should not be taken if they have severe diarrhoea, vomiting (gastroenteritis) or they are dehydrated.
- Report any adverse events to the hospital specialist, where appropriate.

c. Patient

- Discuss potential benefits and side-effects of treatment with the specialist and GP, and to raise any outstanding queries.
- Share any concerns in relation to treatment with aliskiren.
- Report any adverse effects to the specialist or GP whilst taking aliskiren.
- Report to the specialist or GP if he/she does not have a clear understanding of the treatment.
- Participate in the monitoring of therapy and the assessment of outcomes, to assist health professionals to provide effective, safe, appropriate treatment.

13. Contact numbers for advice and support

Post	Telephone
Professor of clinical pharmacology	01223 762578

14. Monitoring compliance with and the effectiveness of this guideline

Clinical pharmacology will regularly review incidents and feedback from GPs with regard to the use of this drug and update the guideline accordingly.

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The information contained in this guideline is issued on the understanding that it is accurate based on the resources at the time of issue. For further information please refer to the most recent Summary of Product Characteristics https://www.medicines.org.uk/emc/medicine/20049