NHS NPC National Prescribing Centre

MeReC Monthly

No.28 July 2010

MeReC Publications

What is the place in therapy of simvastatin 80mg in the light of recent MHRA guidance?

The May edition[1] of Drug Safety Update includes an article advising healthcare professionals that the product information for simvastatin has been updated to highlight the increased risk of myopathy associated with the 80mg/day dose compared with lower doses. This article examines this issue. Further detail is available in MeReC Stop Press Blog No. 1423.

Action

Health professionals should follow NICE guidance on lipid management and use simvastatin 40mg/day for most people for whom lipid-lowering is appropriate to reduce their cardiovascular (CV) risk. **NICE lipid guidance explicitly sets no lipid targets that patients are expected to achieve, for either primary or secondary prevention.** High-intensity statin therapy should not be automatic but may be **considered** in certain circumstances, taking into account the patient's informed preference, including the benefits and risks of treatment. Statin-related myopathy occurs with all statins and appears to be related to dose. **There is no good evidence to suggest that any one statin has any advantages over another in this regard at a population level.**

What does the MHRA say?

The product information for simvastatin now recommends that the 80mg/day dose should be considered only in patients with severe hypercholesterolaemia at high risk of CV complications who have not achieved their treatment goals on lower doses, when the benefits are expected to outweigh the potential risks. Similar changes are being made to the product information for combination products that contain simvastatin. The MHRA advises that prescribers treating patients who are taking simvastatin 80mg/day, or who are being considered for an up-titration to that dose, may need to review their treatment during their next visit, to take into account the new evidence. Patients who are currently taking simvastatin 80mg/day should not stop taking their medicine. However, they should be advised to contact their doctor immediately if they experience unexplained muscle pain, tenderness, or weakness.

The MHRA advice follows consideration of the results of the SEARCH study in patients with a history of myocardial infarction. Over a median of 6.7 years, treatment with simvastatin 80mg/day did not show significant benefits over simvastatin 20mg/day in reducing major CV events. However, myopathy occurred in 0.9% of patients who received simvastatin 80mg/day compared with 0.02% in those taking simvastatin 20mg/day (number needed to harm [NNH] 114; n=12,064). An estimated 0.2% patients in the simvastatin 80mg group developed rhabdomyolysis compared with none in the 20mg group. A previous randomised controlled trial (RCT) found no significant differences in discontinuation rates due to muscle problems with different doses of simvastatin, but more patients in the high-dose group than the low dose group developed myopathy (see the full Blog for details).

What data are there on other statins at high doses?

There are no head-to-head RCTs which compare one statin with another at equivalent doses. As we discussed in a previous blog, statin-related myopathy occurs with **all** statins and the risk increases at higher doses. There is no good evidence to suggest that any one statin has any advantages over another in this regard at a population level when used at equivalent doses. The full blog discusses several RCTs (IDEAL, TNT and PROVE-IT) which compared **high-dose atorvastatin** (80mg/day) with atorvastatin or other statins at lower doses. All found that atorvastatin 80mg/day was associated with more discontinuations due to adverse effects and more patients having raised liver enzymes than the comparator statin.

The MHRA has previously warned about the risk of muscle side effects with **rosuvastatin**: patients should start on 10mg/day (5mg/day for Asian patients and those with pre-disposing factors for myopathy), including patients switched from other statins, and the dose should be titrated up if necessary only after a four week trial.

All information was correct at the time of publication (July 2010)

What does NICE guidance say about statin doses and lipid targets?
NICE guidance on lipid management in people without type 2 diabetes advises that simvastatin 40mg/day should be prescribed for primary and secondary prevention of CV events for most people at risk of CV disease. (If there are potential drug interactions, or simvastatin 40mg is contraindicated, a lower dose or alternative preparation such as pravastatin may be chosen). It is important to note that **NICE lipid guidance explicitly sets no lipid targets that patients are expected to achieve, for either primary or secondary prevention**. It does advise certain lipid levels which may be useful to guide treatment.

Once a person has started a statin for **primary prevention**, repeat lipid measurement is unnecessary. Clinical judgement and patient preference should guide the review of drug therapy and whether to review the lipid profile.

In secondary prevention for patients without acute coronary syndrome (ACS), prescribers should **consider** increasing to simvastatin to 80mg/day, or to a drug of similar efficacy and acquisition cost, **only** in patients whose total cholesterol is greater than 4mmol/L **and also** whose LDL-cholesterol is greater than 2mmol/L. If either figure is below that level, then increasing the dose is not recommended. It is important to note that these are lipid levels which should prompt prescribers to **consider** increasing the dose. They are **not** targets patients are expected to achieve. Moreover, in the full guideline, NICE states that most patients would not have a total cholesterol less than 4mmol/L on simvastatin 80mg/day and recommends against trying to achieve this using higher cost statins such as atorvastatin.

NICE also advises that any decision to offer a higher intensity statin should not be automatic, but should take into account the patient's informed preference, including the benefits and risks of treatment. This is entirely consistent with the recent MHRA guidance.[1]

In people with ACS, NICE found that atorvastatin 80mg/day and simvastatin 80mg/day are both cost effective, **if more intensive statin treatment is chosen**. Again, NICE advises that the decision to offer a higher intensity statin should take into account the patient's informed preference, as above. In addition, NICE **does not** recommend target lipid levels in people with ACS.

NICE guidance on lipid management in people with type 2 diabetes recommends simvastatin 40mg/day as the usual choice and dose of statin, with an increase to 80mg/day if the total cholesterol is more than 4mmol/L **and also** the LDL-cholesterol is more than 2mmol/L on treatment. In people with type 2 diabetes and existing or new CV disease, or increased albumin excretion, NICE advises **considering** intensifying lipid-lowering treatment to achieve a total cholesterol of less than 4mmol/L **or** an LDL-cholesterol of less than 2mmol/L. However, in line with good medical practice, such a decision should take into account the patient's informed preference, including the benefits and risks of treatment.

If statins seem ineffective in lowering cholesterol it is advisable to check the patient's concordance as a first step. It is also important to bear in mind that a single cholesterol reading may over- or under-estimate a person's true average cholesterol by up to 14%. Health professionals should be wary of increasing a patient's lipid-lowering treatment on the basis of a single cholesterol test if they are reasonably confident that the patient is taking the medication as prescribed. This is discussed in a previous blog.

In addition to acting upon this new MHRA advice regarding the risk of myopathy with high dose simvastatin, it is important to note that there are many more primary care prescriptions issued for atorvastatin 10mg and 20mg each quarter than for high-dose statins such as simvastatin 80mg. Since NICE recommends simvastatin 40mg/day as the first-choice statin for most patients, there is significant scope for reviewing patients taking these lower doses of atorvastatin and, where appropriate, revising their treatment to ensure this is in line with NICE guidance.

For further details, including a discussion of the role of ezetimibe, and management of familial hyperlipidaemia, please see MeReC Stop Press Blog No. 1423. More information on high-dose statin therapy and lipid management in general can be found on the lipids floor of NPCi.
medical journals.

Reference

1. MHRA. Simvastatin: increased risk of myopathy at high dose (80mg). Drug Safety Update. May 2010;3(10):7–8

Comparative safety of ICS/LABA combinations in chronic asthma

A Cochrane review[1] found no significant difference in serious adverse events when different combinations of inhaled corticosteroids and long-acting beta2 agonists were compared in people with chronic asthma. However, as these events were rare, there was insufficient evidence to know for certain whether regular formoterol and budesonide (or formoterol and beclometasone) has an equivalent, or different, safety profile from salmeterol and fluticasone. There were little comparative safety data on formoterol and beclometasone (Fostair▼), and no data available in children.

Action

Health professionals should follow the British guideline on the management of asthma. For adults, adolescents and children aged ≥5 years, who are not adequately controlled on an inhaled corticosteroid (ICS) alone (step 2), the addition of a long-acting beta2 agonist (LABA) should be considered on an individual trial basis (step 3). However, before starting a new drug or stepping up treatment, the patient's understanding of the role of treatment, adherence to treatment, inhaler technique, and appropriate elimination of trigger factors should be confirmed. Control of asthma should be assessed after an agreed duration, depending on the desired outcome, and the LABA discontinued in the absence of benefit. The Commission on Human Medicines' advice on the use of formoterol and salmeterol in asthma should be followed.

If treatment with an ICS and LABA is considered appropriate, NICE recommends that the decision to use a combination device or separate devices should be made on an individual basis, taking into consideration therapeutic need and the likelihood of treatment adherence. If a combination device is chosen, then the least costly device that is **suitable for the individual** is recommended.

Many patients with asthma may be over-treated. It is important to note that, switching patients from one combination device to another, for example on cost-grounds, is not a simple switch programme. Clinicians should focus on ensuring that patients are reviewed regularly, with a view to stepping down therapy when asthma control is achieved and stepping up therapy when it is not.

For more details on this Cochrane Review and what it means in practice as well as a discussion on the choice of combination treatment and role of Fostair▼ (formoterol and beclometasone) see MeReC Rapid Review Blog No. 1474.

Reference

1. Cates CJ, Lasserson TJ. Regular treatment with formoterol and an inhaled corticosteroid versus regular treatment with salmeterol and an inhaled corticosteroid for chronic asthma: serious adverse events. Cochrane Database of Systematic Reviews 2010, Issue 1. Art. No.: CD007694. DOI: 10.1002/14651858.CD007694.pub2

Measuring blood pressure — who does it, and how it is done, really matter

This Australian observational study[1] found that blood pressure (BP) measured in clinic by trained staff using meticulous technique was higher than ambulatory BP values by an average of 6/3mmHg. BP measured in clinic by referring doctors was higher still, by an average of 9/7mmHg compared with readings taken by trained staff.

Action

This study suggests that clinic measurements of BP made by doctors are substantially higher than 'gold standard' clinic measurements made by staff trained in measurement of blood pressure. If confirmed, this could have profound implications for diagnosis and treatment. The suggested ambulatory BP thresholds and targets equivalent to targets in guidelines for clinic-measured blood pressure may be useful for specialists. However, NICE guidance does not recommend routine use of automated ambulatory BP monitoring (or home monitoring devices) in primary care, because their value has not been adequately established. Health professionals should use meticulous technique when measuring blood pressure in accordance with NICE guidance and MHRA advice. See MeReC Rapid Review Blog No. 1342 for further details.

Reference

1. Head GA, et al. Definition of ambulatory blood pressure targets for diagnosis and treatment of hypertension in relation to clinic blood pressure: prospective cohort study. BMJ 2010;340:c1104

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