UPDATE
Module 1646

This module covers:

- Key possible side effects of statins, including myopathy, poor cognition, eyesight problems and depression
- How to identify potential side effects and when to refer for further investigation
- How comorbidities, lifestyle and liver and thyroid function can affect statin therapy

MARCH

Cardiovascular month

Statins: six case studies	March 2
Myocardial infarction 1	March 9
Myocardial infarction 2	March 16
Hypertension	March 30

Statins: six case studies

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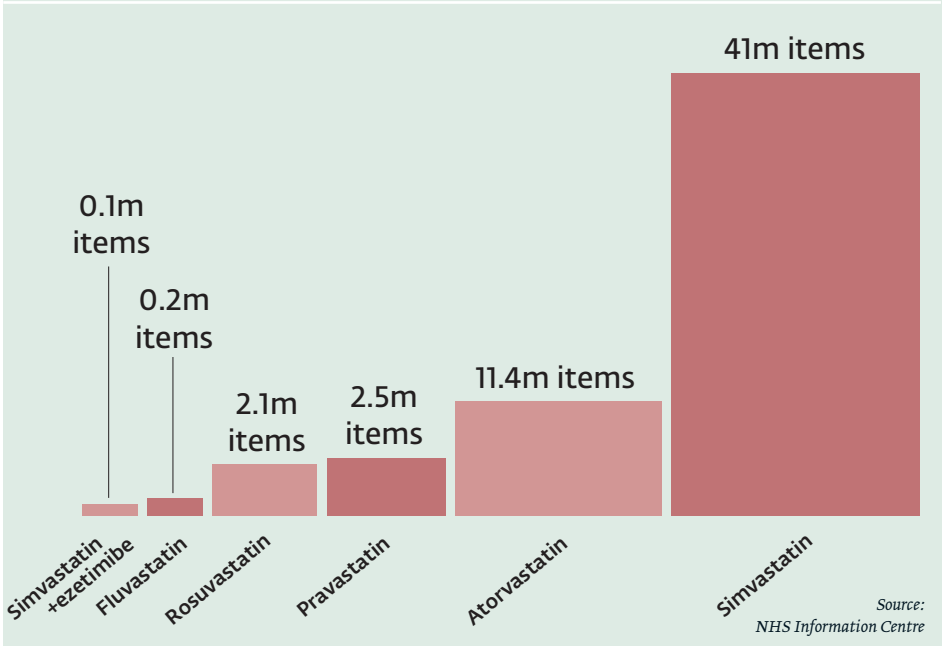
Blood cholesterol is a key modifiable risk factor for coronary heart disease and cholesterol levels can be reduced by dietary change, physical activity and drugs such as statins. Statins reduce the risk of cardiovascular disease (CVD) events, irrespective of serum cholesterol concentration, and are the drug of choice for primary and secondary prevention of CVD.

A recent British Heart Foundation report highlighted that around 60 million prescriptions were written in 2011 in the UK for statins (see right).[1] Nice recommends the use of statins in its national guidance for all patients who have established CVD and as primary prevention for people at increased risk of CVD.[2]

Yet statins are not without their problems. This article will look at presentations in the pharmacy of some of the adverse effects of statins through a case study approach.

Statin prescribing in England, 2011



Case study 1

EDWARD HARDY

AGE: 45 years

PRESENTATION: Edward has been diagnosed as having a familial lipid disorder. His brother recently had a fatal myocardial infarction aged 50 years. He has been taking atorvastatin 80mg for the past six weeks. He asks to speak to the pharmacist about the thigh pain he is experiencing.

Discussion

Myopathy is a side effect associated with all statins, although lipophilic statins (simvastatin and atorvastatin) may potentially cause problems because they penetrate the muscle tissue.[3] The precise mechanism underpinning this adverse drug reaction is unknown.

Myopathy is used as an umbrella term for a number of muscle disorders, including myalgia and myositis (inflammation of the muscles). In practice, symptoms include fatigue, muscle pain, muscle tenderness, muscle weakness, nocturnal cramping and tendon pain. The muscle symptoms tend to be worse when the person exercises.

Statins should be used with caution in patients with an increased risk of muscle toxicity, including those with a personal or family history of muscular disorders, previous history of muscular toxicity, a high alcohol intake, renal impairment, hypothyroidism and the elderly.

When a patient reports muscle ache, creatine kinase (CK) levels should be checked. If significantly raised (some sources say 10 times the upper limit of normal, the BNF suggests five), then the statin should be stopped. This is because of the risk of rhabdomyolysis, the breakdown of muscle fibres, leading to the release of muscle fibre contents (myoglobin) into the bloodstream. Myoglobin can cause kidney damage.

While statin therapy is stopped, the patient should be monitored for muscular symptoms and cardiovascular risk. If the symptoms resolve and CK levels return to normal, reintroduction of the statin or introduction of an alternative statin may be considered. This should initially be at the lowest dose and with close monitoring.

However, if CK levels are normal or minimally raised, then a dose reduction or an alternative statin may be tried. It is not uncommon for patients to experience muscle problems in the absence of raised CK; in some cases statins cannot be tolerated and an alternative anti-lipid agent has to be chosen.

Action points

Edward should be referred to his GP for a blood test. In Edward's case, the myopathy is found not to be related to raised CK. His dose is reduced to 40mg. The muscle pains continue however, and he is switched to simvastatin, which he appears to tolerate.

Case study 2

LOUIS HEALEY

AGE: 57 years

PRESENTATION: **Mr Healey had a myocardial infarction a week ago. Recently discharged, he talks to you about his medicines. "The hospital have told me I also need to have a statin, but they did not give it to me because one of my blood tests was raised – something to do with my thyroid. The GP has started me on thyroxine and once things settle down, I can start the statin. Is that right?"**

Discussion

Low thyroid levels can lead to high cholesterol readings. Most people who have had a heart attack will end up taking a statin, but in Mr Healey's case his cholesterol level can only be assessed properly once his hypothyroidism has been corrected.

Action points

Explain to Mr Healey why the doctor wants to sort out his thyroid condition before deciding which drug and dose to give him. Also explain that untreated hypothyroidism increases the risk of muscle side effects with statins.

Case study 3

DOMINIC LEGGE

AGE: 55 years

PRESENTATION: **Dominic has angina, hypertension, is overweight and drinks alcohol to a hazardous level. He has been taking simvastatin 80mg for two years. He had a recent blood test result that indicated raised liver enzymes, so his GP reduced the statin dose to 40mg. Although it has now returned to normal, the doctor has left the simvastatin at the lower dose as a precaution. Dominic asks why this has been done and if this puts him at increased risk of a heart attack.**

Discussion

All statins are associated with an increased risk of liver dysfunction, although there are differences in hepatotoxicity between agents, with fluvastatin appearing to carry the highest risk.

The BNF advises the cautious use of statins in people with liver disease and/or high alcohol intake. It suggests liver function tests are carried out for all patients at onset of statin therapy, within three months of starting and at 12 months, unless symptoms are suggestive of hepatotoxicity.

However, the US Food and Drug Administration (FDA) has recently removed the requirement for routine monitoring of liver enzymes in patients taking statins.[5] This is because it believes the incidence of statin-induced liver injury is very rare and that routine periodic monitoring of serum alanine aminotransferase (ALT) does not appear to detect or prevent serious liver injury in association with statins.

Action points

The raised liver enzyme may have been an isolated result, however Dominic's high alcohol intake may put him at increased risk of liver damage. It is difficult to gauge the precise effect of halving his statin dose. He is now taking the recommended starting dose for secondary prevention, although this may not reduce his cholesterol level by a desired amount.

If his cholesterol level rises significantly again on the 40mg dose, the GP may decide to increase the simvastatin dose once more and monitor the liver enzymes, or he may try an alternative agent. Nice recommends fibrates, anion exchange resins, nicotinic acid and ezetimibe as second line agents where statins are not tolerated.

Case study 4

PATRICK GREENE

AGE: 91 years

PRESENTATION: **Mr Greene was recently found to have raised cholesterol. Since starting taking a statin, he has been far less active than usual and complaining of feeling unwell so he stays at home. He has had diarrhoea and disturbed sleep, and has been feeling depressed. He does not know why the GP prescribed him a statin, but so far has been compliant with his treatment.**

Discussion

Diarrhoea and insomnia are both recognised statin side effects, as is depression. However, Mr Greene's low mood may relate to his isolation, as he is now unable to get out and about, and to his difficulty sleeping.

Action points

Speak to the GP. Although older patients are equally entitled to preventative medicine as younger ones, Mr Greene had a good quality of life until he started taking the statin and is now virtually housebound. A decision has to be made balancing the statin effects with quality of life and, given the side effects Mr Greene is experiencing, it seems preferable for him to stop taking the treatment.

Case study 5

MOUSSA ALI

AGE: 68 years

PRESENTATION: **Mr Ali has type 2 diabetes, hypertension and is overweight. His GP has decided he is at high risk for a cardiovascular event and started him on a statin six months ago. His wife is worried Mr Ali is becoming forgetful and may be developing dementia. The couple are also concerned his six-monthly blood glucose levels seem to be worsening.**

Discussion

Post-marketing adverse event reports have identified ill-defined memory loss or impairment in people older than 50 years taking statins.[4] The effect can arise within days of starting statin therapy, but may occur years after statin exposure. It is reversible on cessation of the statin.

The cases did not appear to be associated with fixed or progressive dementia, such as Alzheimer's disease. No one statin appears any worse than any of the others and there is no link to patient age or concomitant medication.

Statins have been shown to cause an increase in diabetes incidence and the BNF advises that they can cause hyperglycaemia.

Action points

The GP talks through his findings with Mr and Mrs Ali and they decide that they will monitor the memory loss and discuss the blood glucose levels with the nurse when he next attends the surgery.

Case study 6

DOROTHEA DEAN

AGE: 75 years

PRESENTATION: **Dorothea was put on a statin last year following a stroke. During an MUR she says she believes the statin is working well for her because her cholesterol has gone down significantly. Her main concern is her eyesight; she is finding it difficult to differentiate between colours, finds the glare from bright lights disturbing and is struggling to read.**

Discussion

From her symptoms, Dorothea may be developing cataracts. This could be an age-related issue, as more than half of all people over the age of 65 years will have some form of cataract development in one or both eyes. However, all statins are associated with an increased risk of cataract formation. The effect is unlikely to be dose-related. The risk is significantly increased within a year of starting statins and returns to normal within the first year after stopping treatment.[4]

Action points

Dorothea should be referred to her GP, who may in turn refer her back to the stroke care department at the hospital. Dorothea is later prescribed ezetimibe as an alternative, and her cataracts improve over the next six months.

References

1. British Heart Foundation. *Coronary Heart Disease Statistics*, 2012. BHF, December 2012.
2. Nice. *Lipid Modification CG67*. Nice 2010.

3. Sathasivam S and Lecky B. Statin induced myopathy. *BMJ* 2008;337:a2286.
4. Hippisley-Cox J and Coupland C. Unintended effects of statins in men and women in England and Wales: population based cohort study using the QResearch database. *BMJ* 2010;340:c2197.
5. Food and Drug Administration. *Drug Safety Communication: Important safety label changes to cholesterol-lowering statin drugs.*

Tips for your CPD entry on the side effects of statins

Reflect **Which patient groups are at increased risk of muscle toxicity if they are taking statins? How often should patients taking statins have a liver function test? How does hypothyroidism affect cholesterol test results?**

Plan **This article discusses the side effects of statins and how to identify them, using case studies as examples. It includes information about side effects such as myopathy, raised liver enzymes, cataracts, memory loss, hyperglycaemia, diarrhoea, insomnia and also the effect of thyroid disease on cholesterol test results.**

Act **Read the article and the suggested reading (online), then take the 5 Minute Test (below). Update subscribers can then access their answers and a pre-filled CPD logsheet.**

Find out more about statins and their side effects from the NHS Choices website
http://tinyurl.com/statins1
Read the MUR tips for statins on the C+D website. Identify any patients who might benefit from an MUR or advice about statin side effects when they present with a prescription
http://tinyurl.com/statins2
Think about other advice you could give to patients taking statins, avoiding grapefruit juice for example. The British Heart Foundation has a useful information sheet for patients
http://tinyurl.com/statins3

Evaluate **Are you now confident in your knowledge of the side effects that can be caused by statins? Could you identify at-risk patients and provide advice and sources of further information?**

5 minute test

■ Sign up to take the 5 Minute Test and get your answers marked online: www.chemistanddruggist.co.uk/update

Take the 5 Minute Test

1. Nice recommends the use of statins for all patients who have established cardiovascular disease.
True or false?
2. Patients with renal impairment, hypothyroidism or a high alcohol intake have an increased risk of muscle toxicity with statins.
True or false?
3. Patients experiencing muscle pain with statins may also have raised creatine kinase levels.
True or false?
4. The BNF suggests liver function tests are carried out monthly for the first year of taking statins.
True or false?
5. Nice recommends fibrates, anion exchange resins, nicotinic acid and ezetimibe as second-line agents where statins are not tolerated.
True or false?
6. The risk of cataract development with statins has been shown to be dose-related.
True or false?
7. Statins can cause irreversible memory loss or impairment in people over 50 years.
True or false?
8. Statins have been shown to cause an increase in diabetes incidence.
True or false?
9. Hyperthyroidism can lead to high cholesterol readings.
True or false?
10. Statins can be the cause of insomnia and depression.
True or false?