

Monitoring Patients on Lipid-Lowering Therapy

Introduction

The most commonly prescribed treatments for cholesterol are the statins (HMGCoA Reductase inhibitors) which inhibit endogenous production of LDL Cholesterol and also up regulate its uptake by the liver. The only other therapy in routine use and suggested by NICE is Ezetimibe. Other medication includes; Fibrates (especially if triglycerides are >10mmol/l), Omacor and Bile acid sequestrants but are not for routine use.

Overview of monitoring

TEST	Initial investigations	Monitoring on treatment
Fasting Lipid Profile	✓ At least once before treatment commenced.	Dependent on reason for Rx Primary prevention patients may be adequately monitored by annual Chol/HDL.
Fasting glucose	✓	See below
TSH	✓	
ALT	✓	✓ Once at 3 months and 12 months Further testing only required if clinically indicated
U&E	✓	
CK	X (except high risk groups or myalgia)	Only if myalgia or high risk
INR	✓ If taking warfarin	Close monitoring if on warfarin with any dose adjustments or prescribing of interacting medications.

1. Fasting lipid profile

NICE guidance suggests screening and monitoring with cholesterol and non HDL, but at least once a fasted lipid profile should be tested before commencing medication. This is to recognise monogenic dyslipidaemias. A fasted lipid profile should include cholesterol, HDL, non-HDL and triglycerides.

Those patients with monogenic disorders such as Familial Hypercholesterolaemia and in secondary prevention require a fasted lipid profile for monitoring. Minimum retesting interval 3 months but most will have annually.

2. Fasting Glucose, TSH, U&E

NICE guidance recommends screening with TSH, fasting glucose and U&E before initiation of medication. This is to rule out secondary causes of dyslipidaemia (diabetes, hypothyroidism and renal disease). Ideally a urine albumin: creatinine ratio should be sent to complete the renal screen.

Reduced eGFR

Statins	Avoid high doses in mild renal impairment. Avoid use when eGFR <30 ml/min/1.73m ² .
Fibrates	Dose should be reduced when eGFR < 60 ml/ min/1.73m ² . Avoid use when eGFR <40 ml/min/1.73m ² .

Fasting glucose

Some evidence suggests that statins raise blood glucose and in some patients, at high risk of future diabetes, may produce a level of hyperglycaemia where formal diabetes care is appropriate. This risk, however, is outweighed by the reduction in vascular risk with statins and therefore should not be a reason for stopping statin treatment. Patients at risk (fasting glucose 5.6 to 6.9 mmol/L, BMI>30kg/m², raised triglycerides, hypertension) should be monitored both clinically and biochemically according to national guidelines. Routine glucose or HbA1c monitoring is not required.

3. ALT and Liver function

There is guidance regarding statins. For other medication see BNF.

Baseline

- Caution when prescribing statin or fibrate with a history of heavy alcohol ingestion or a past history of liver disease.
- A baseline LFT is still advised.
- ALT < 3x ULN, Statin therapy should not be withheld.
- ALT > 3x ULN, Statins should not be started. A repeat to assess the trend is advised. If persistently elevated a full liver screen should be instigated to investigate the aetiology. If the final diagnosis is fatty liver disease statins may still be warranted.

Monitoring

- NICE suggest LFTs should be checked within 3 months and 12 months after commencing medication. Routine monitoring thereafter in patients on statins is not recommended unless clinically indicated or if the statin is given in combination with fibrate therapy.
- If ALT > x3 ULN withhold statin and assess the trend in ALT. If the ALT normalises the statin may be tried again however a dose reduction or alternative statin could be considered.
- If the ALT remains > 3 x ULN a full liver screen should be carried out to investigate the aetiology.

*Note cholestatic jaundice has been described in patients on statin therapy.

4. Creatinine kinase

Consideration prior to treatment;

- An informed discussion with the patient regarding the risks versus benefits of treatment is required prior to prescribing treatment. This will involve discussion and assessment regarding the risk of myositis.
- Caution should be exercised in patients with pre-disposing risk factors for rhabdomyolysis. The Committee on Safety of Medicines recommends that baseline CK levels are measured prior to commencing statin therapy in the following situations:
 - Elderly (age \geq 65 years)
 - Renal impairment
 - Uncontrolled hypothyroidism
 - Personal or familial history of hereditary muscular disorders
 - Previous history of muscular toxicity with a statin or fibrate
 - Alcohol abuse
 - Concomitant use of other lipid lowering agents i.e. fibrates or nicotinic acid
 - Concomitant use of cytochrome P450 3A4 inhibitors including macrolide antibiotics, cyclosporin, azole antifungals (e.g. ketoconazole and itraconazole) and protease inhibitors
 - Current myalgia
- If baseline CK is >5 times the upper limit of normal (ULN) at baseline then treatment with a statin should not be commenced.

Role in monitoring treatment;

Routine monitoring of CK in asymptomatic patients is unnecessary

CK is only recommended if the patient is symptomatic. Either myalgia or weakness should prompt testing. (Also helpful to check TSH if thyroid status unknown).

1. If CK normal no further testing is recommended.
If symptoms of myalgia are tolerable and the drug has already been stopped, the same agent or another could be re-started.
2. If CK greater than 5 x ULN (i.e. approximately 1,600 iu/L in men, 1,000 iu/L in women), rhabdomyolysis is present, discontinue therapy. Monitor patient, including renal function.
If symptoms resolve and CK level returns to normal, it is worthwhile considering re-introducing a different statin preparation, initially at a low dose. Monitor patient monthly.
3. If CK less than 5 x ULN, continue medication if muscle related symptoms are tolerable, check CK every 3 months and if CK remains stable check 6-monthly to annually thereafter. Patient may prefer to try alternative statin.

4. Risk of myopathy is increased if patient aged >80 years, renal impairment, hypothyroidism, muscle disorders or alcohol abuse. Genetic factors are also important. Also, with concurrent administration of fibric acid derivatives, cyclosporin, some antidepressants, erythromycin, niacin or azole antifungals. In these circumstances CK should be monitored if any musculoskeletal symptoms are reported.
5. If muscle-related symptoms or raised CK persist after statin therapy is stopped, consider further investigations such as B12, TFT, inflammatory markers, AIP, electromyography and muscle biopsy.
6. Note macro-CK, a complex formed between CK and IgG, is present in 1-2% healthy population. This can cause an elevated CK result. Examination for the presence of macro-CK should be considered.

4. Anticoagulant therapy

Monitor INR prior to commencing a statin, fibrate or Omacor and around the time of dose adjustments.

If prescribing drugs which may also induce or inhibit cytochrome P450 3A4 increased INR monitoring or statin withdrawal is needed

References

- 1 Statin induced myopathy (Clinical Review). *BMJ* 2008; 337: 1159-1162
- 2 British National Formulary, No. 58, September 2009. bnf.org
- 3 Lipid Modification Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. NICE Clinical Guideline 181. www.nice.org
- 4 Committee on Safety of Medicines, Medicines Control Agency. HMG CoA reductase inhibitors and myopathy. *Current problems in Pharmacovigilance* 2002; 28:8-9
- 5 Final conclusions and recommendations of the National Lipid association statin safety assessment task force. *j.amjcard.*2006.02.030. McKenney et al
- 6 Electronic medicines compendium