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Statins: adherence and side-effects

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Abstract

Many patients either do not adhere to, or fail to persist with, long-term lipid-lowering therapy. This unfavourable medication utilisation behaviour compromises potential treatment benefit. In retrospective studies, patients aged 50-65 had the highest adherence rates, while both younger and older patients had lower rates. Patients with pre-existing cardiovascular disease adhere better than those in primary prevention. Financial barriers may impair adherence. At the individual patient level, health beliefs, perceptions of own cardiovascular risk and need for medication, concerns about side-effects and inconvenience of treatment may influence adherence. In clinical trials, regular reminders to patients have been shown to improve adherence, but each patient will require an individually tailored treatment strategy.

Myopathy is the most common clinically relevant adverse effect of statins. The clinical severity of statin myopathy is highly variable, ranging from mild muscle ache to rare instances of rhabdomyolysis. Risk factors for statin myopathy include age, statin dose, hypothyroidism, medications that inhibit statin metabolism, combined statin and fibrate therapy, and renal impairment. Alternative causes of myopathy should be excluded before muscular symptoms are ascribed to statins. The management of statin myopathy is guided by the severity of symptoms and the creatine kinase level. Potential management strategies include statin dechallenge and rechallenge, statin dose reduction, statin switching, non-daily dosing and use of alternative lipid-lowering agents, such as ezetimibe.

Statins rarely cause severe liver disease. Mild liver enzyme elevations are seen relatively frequently in patients starting statins, but are usually not clinically important. Patients with persistently elevated liver enzymes should be investigated to determine the cause of liver disease. Patients with stable, well-compensated liver disease can be prescribed statins, provided they are closely monitored.

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Introduction

"Drugs don't work in patients who don't take them." Former US Surgeon General, C Everett Koop

Lipid-lowering medication, in conjunction with a healthy lifestyle, can significantly reduce the risk of cardiovascular disease. However, poor adherence (adherence is defined as taking the medication correctly and regularly, according to the instructions provided) and low rates of persistence (persistence with lipid-lowering medications is defined as continuing indefinitely) result in many patients not benefiting optimally. Failure to take lipid-lowering medication may result in the occurrence of preventable cardiovascular events in those for whom the primary goal of therapy is cardiovascular risk reduction. Patients who are being treated primarily for the control of severe hypertriglyceridaemia may experience potentially fatal acute pancreatitis. Improving adherence and persistence with medical therapy has the potential for great benefit, but is often difficult to achieve.[1] According to a recently published mathematical model of statin use in a population,[2] specifically increasing statin persistence from 50-75% at five years, would prevent more cardiovascular events than lowering the risk threshold for prescribing statins. Spending more on lipid-lowering drugs does not prevent more events if patients do not actually take the drugs, or only take them for a few months.

In everyday clinical practice, persistence rates with lipid-lowering medication and other chronic medications are low.[3,4] In a study of patients over the age of 65 years, only 25% of patients continued to collect more than 80% of their medication supplies five years after statin therapy was initiated. Most patients discontinued treatment early, as evidenced by a six-month persistence rate of only 56%.[3]

The reasons for nonadherence and nonpersistence are complex, and differ in each patient. This article will briefly review information on statin adherence and persistence, and then discuss some of the more common adverse effects of statins.

Adherence and persistence

It is perhaps not surprising that long-term persistence with lipid-lowering medication is so low. Dyslipidaemia is usually asymptomatic until complications set in. Lipid-lowering medications do not improve well-being, and at best, treated patients will feel no different. Some may even experience significant side-effects. Therefore, treatment of hyperlipidaemia usually involves asking patients to take long-term medication for a symptomless condition. Those who do not take their medication suffer no immediate consequences, except where there is severe hypertriglyceridaemia. Patients who fail to take their treatment for asthma, arthritis or reflux, to name only a few examples, do not feel well after a short period of non-adherence, and usually resume treatment.

In observational studies, statin adherence is associated with markedly reduced rates of cardiovascular disease, with the achieved event reduction often exceeding that seen in randomised clinical trials.[5-8] However, this marked benefit is not entirely ascribable to lipid-lowering medication, as patients who adhere better are more likely to engage in other healthy behaviour. They are the so-called "healthy users".[9] This is well exemplified in a recent study that showed that statin-adherent patients were less likely to be involved in traffic or workplace accidents, used screening services more frequently, and had a lower likelihood of developing diseases with no biological link to statin adherence.[10] Nonadherers do not only forego protection from statins, but also have riskier lifestyles.

Predictors of statin nonadherence

All studies on adherence are bedevilled by the methodological problem of measuring adherence accurately. Most rely on large medical funder databases, and quantify adherence by the number of prescriptions filled in a given time period. Of course, the fact that the patient collected the medication does not prove that it was taken, and patients who did not claim from their medical funders may have bought medicines privately. Nevertheless, pharmacy records are a reasonable proxy for adherence, as it is impossible and very intrusive to directly document adherence in large groups of patients. A recent meta-analysis of such record-based studies on statin adherence identified several predictors of poor adherence.[11]

The relationship between age and statin nonadherence is U-shaped. The nonadherence rates in patients younger than 50 years are higher than those in patients aged 50-65 years. Adherence is best in this middle-aged group, and then decreases again with increasing age.[11] Patient perception of cardiovascular risk may well influence adherence, with younger patients often perceiving themselves at lower risk, while heart disease is more of a reality for middle-aged adults. Low adherence rates in those over 70 years are probably multifactorial, with depression, polypharmacy, financial barriers and cognitive impairment all potentially contributing.

Female gender predicts nonadherence (relative risk 1.07; 95% confidence interval 1.04-1.11) in the majority of studies.[11] Women access health care more frequently than men, and tend to pay more attention to their health.[12] Their lower reported adherence rate may reflect increased concern about side-effects, or a lesser perceived risk of heart disease, which is still often viewed as a predominantly male problem.

Financial barriers are well known to influence adherence negatively. As out-of-pocket costs increase, adherence declines.[13] Higher income is associated with lower rates of nonadherence in healthcare systems in which patients have to buy their own medication, or have to contribute to the cost.[11]

Patients who have experienced a cardiovascular event are more likely to adhere to statins than those with additional risk factors, such as diabetes or hypertension. These patients correctly perceive themselves to be at increased risk, and are more likely to be motivated to continue taking statins.[11]

Patients taking other noncardiovascular medications are less likely to adhere to statins. This may be due to the increased complexity of their medication regimen and perceived lower benefit of statins when compared to medications directed at specific symptoms.[11] Interestingly, a study that examined prescriptions in more detail, found that an increasing number of cardiovascular medications correlated with better adherence.[14] Patients taking more cardiovascular medications are most likely to be sicker and at higher cardiovascular risk, and therefore perceive a greater benefit from taking satins.

The demographic results from database-based studies can be used to identify patient populations that are at high risk of nonadherence, and who may benefit from additional counselling and monitoring. They do not solve the clinician's dilemma of assessing the risk of and preventing nonadherence in the individual. Individual determinants of nonadherence are less well studied, but may include health beliefs, perceptions of the health system, self-efficacy, concerns about side-effects and depression.[15]

Members of a large American health maintenance organisation (Kaiser Permanente), that had a gap of at least one month in their statin supply, were invited to participate in focus groups to explore their reasons for nonadherence.[16] In this relatively small study of 18 patients, 15 different reasons for not taking statins were identified.

The reasons can be grouped into four main categories:

- ***Concern about, or experience of, adverse effects***: Very few patients suffered adverse effects, but concern was generated by reading package inserts, listening to friends and family, and searching the Internet.
- ***Uncertainty about the benefit of, or need for, statins***: Some patients stated that due to having high cholesterol, the lack of symptoms made them uncertain as to whether they actually needed treatment.
- ***Lack of convenience***: This accounted for a few discontinuations, with some patients stating that they did not like spending time collecting their medication and presenting for follow-up tests.
- ***Other reasons were varied***: These included the desire to take a brand-name statin rather than a generic; being too ill to take the statin; and an unwillingness to stop drinking grapefruit juice. Taken in large quantities, grapefruit juice inhibits the metabolism of some statins.

In this study, financial concerns were not prominent. All patients were insured and the required co-payment for statins was minimal.

Patients were asked to identify factors that might help them improve their adherence. Many expressed a need to know more about statins, alternative therapies and statin side-effects. Patients wanted longer consultations, more regular follow-ups, and regular reminders from their doctors.

In another study of factors influencing statin adherence, 313 Finnish patients with cardiovascular disease were presented with three different statements on statin therapy, and asked what their self-estimated adherence rate would be after listening to each of the three statements.[17] The aim of the study was to determine how much information doctors should give patients about statins and their effects on cardiovascular outcomes. Each statement gave more detailed and complex information on the beneficial effects of statins with regard to cardiovascular outcomes.

The three statements were:

1. Your cardiologist recommends this medication as it reduces your risk of myocardial infarction.
2. Within a period of five years, this medication will reduce the risk of death caused by heart disease by 42%, and the risk of myocardial infarction by 34%.
3. Without this medication, 88% of patients will still be alive after five years. Of those using the medication, 91% will survive. The risk of myocardial infarction is 20% if one uses the medication, but 29% for those not using the medication.

Statement 3 describes the benefits of statins most accurately as it presents the absolute risk reductions within a given time frame, yet most patients thought that they would be most likely to take the statin following a simple recommendation from their cardiologist (Statement 1). In an earlier part of the questionnaire, most patients indicated that they wanted detailed information about their treatment and the expected benefits. Therefore, patients' reactions to being given the detailed information that they requested is not always easy to predict. Some may have struggled to understand the detailed information, resulting in most of them indicating that they thought a clear, simple recommendation from their cardiologist (Statement 1) would "work best" for them. This study should not be taken to support a paternalistic "doctor knows best" attitude, but it serves as a worthwhile reminder that the information supplied should be tailored for each patient individually, with the patient indicating what level of detail he or she desires.

Improving statin adherence and persistence

Patients currently taking statins are more likely to persist with their medication than those who initiated statin therapy a decade ago, but statin persistence remains far from satisfactory.[18,19] Improving adherence and persistence remains a major clinical challenge. Interventions to improve lipid-lowering medication adherence were examined in a recent Cochrane review.[20]

Possible interventions aimed at improving adherence could include a simplified drug regimen, increased patient education and information, intensified patient care, with more frequent follow-up and medication reminders, complex behavioural interventions such as group sessions, decision support systems for doctors, and improved administrative efficiency. The first four interventions have been studied either alone, or in combination, in a total of 11 randomised controlled trials.

Patient reminders and treatment re-enforcement was studied in six studies, and found to be effective in most. The studied interventions included regular telephone calls by a practice nurse, regular review by a community pharmacist, and providing a medication calendar when patients filled their first prescription. The absolute increase in adherence was mostly modest, but large enough to reach statistical significance. Other potential interventions have not been as extensively evaluated, and lack published evidence of benefit.[20,21]

The Adherence Estimator is a brief questionnaire that can be applied in everyday clinical practice to assess the risk of nonadherence in a given patient.[22]

The questionnaire assesses the patient's perception of treatment in three critical areas: the need for medication, concern about medication, and affordability of medication.

These areas can also be covered informally when discussing treatment with the patient. If the patient perceives any one of these treatment aspects negatively, then the risk of nonadherence is high, and additional information and an explanation should be offered. Patients should be offered follow-up appointments, and receive treatment reminders where feasible. However, in clinical practice there is not a single solution that works for all patients, and judging which information and support each patient needs to ensure that he or she continues to take his or her medication, falls more within the "art of medicine" than the "science of medicine".

Adverse effects of statins

Searching Google for "statin side-effects" returns more than half a million hits. Separating fact, fiction and speculation is almost impossible for the lay reader. Take, for example, the often-claimed link between statins and motor neuron disease.[23,24] Motor neuron disease is a rare disorder, but statins are prescribed to millions of patients, so it is expected that some patients on statins will develop motor neuron disease. The critical questions are whether the rate in patients taking statins is higher, and whether this is due to the statin itself, or whether statin users are affected by other characteristics that increase the likelihood that they will develop motor neuron disease. Proving or refuting the association beyond doubt, using the limited data available, is almost impossible. From the available data, one can only conclude that if statins have an effect on increasing the risk of motor neuron disease, it is very small.[24] This article will not review all the potential adverse effects of statins, but will focus on myopathy and hepatotoxicity. For a comprehensive review of all adverse effects attributed (with varying degrees of plausibility) to statins, see the article by Golomb and Evans. This article has 892 references.[25]

Muscle-related problems

Statin-related muscle problems are the most common adverse effect of statin therapy. Although there is no universally accepted definition of statin myopathy, generally, the following categorisation is used clinically.[26] Myopathy is an overarching term that describes all statin-related muscle disorders. While myalgia is muscle pain without elevation of the creatine kinase (CK), myositis is muscle pain with enzyme elevation, and rhabdomyolysis is characterised by extreme CK elevation [usually more than ten times the upper limit of normal (ULN)], with a rise in creatinine and positive urine myoglobin.

The reported incidence of myopathy in clinical studies is often no different between patients allocated statins and those on placebo.[27] However, some epidemiological studies report myopathy rates to be as high as 5-10%.[28,29] Many trials exclude patients at high risk of myopathy, especially those with previous myopathy, and with a statin run-in period. Statin-intolerant patients are excluded from randomisation. Furthermore, many trials only report myositis with CK elevation, rather than myalgia, which is much more common. Therefore, statin myopathy is more common in clinical practice than suggested by trial data, but the rates of rhabdomyolysis are very low (about 0.1-0.2 cases per 1 000 person years) in all types of studies.[30]

Patients with statin myopathy commonly complain of muscle pain that is most prominent around the hips and shoulders, but may involve any muscles. The pain is often described as aching, heaviness, tiredness or cramping, often in association with stiffness. The intensity of the pain can be quite variable, ranging from a mild ache to incapacitating pain that confines patients to bed. Myopathy often occurs soon after treatment initiation, but may occasionally occur after a long lag period. Symptoms usually improve rapidly, within days, when statins are stopped (dechallenge). Patients with persistent symptoms, elevated CK, and especially weakness after statin withdrawal, should be evaluated further, as many of them have undiagnosed neuromuscular disorders.[30,31] See Table I for risk factors for statin myopathy

Table I: Risk factors for statin myopathy[30]

Patient-related	Treatment-related
Advanced age	Statin dose
Female sex	
Low body mass	[a]Concomitant medications
Frail with multi-system disorders	Fibrates
Hypothyroid	Cyclosporin
Alcohol abuse	Antifungals
Very active physically	Macrolide antibiotics
[b]High intake of pure grapefruit juice	HIV protease inhibitors
Previous statin myopathy	Nefazodone
Unexplained CK elevation	Amiodarone
Family history	Verapamil
Postoperative period	
[c]Genetic factors	

a = Interactions vary according to the statin prescribed. Not all statins interact with all medications in the list. Lovastatin, simvastatin, and to a lesser extent, atorvastatin, are highly reliant on CYP3A4 hepatic isoenzyme metabolism. Most enzyme inhibitors inhibit the CYP3A4 isoenzyme, and the abovementioned statins are frequently involved in drug interactions
b = Most grapefruit juice sold in South Africa is not pure, but manufactured using deflavoured apple or grape juice as a base
c = Polymorphism in SLCO1B1 (an organic anion-transporting polypeptide) has been associated with simvastatin-related myopathy.[32]

The management of statin-related myopathy can be difficult and frustrating at times. There are guidelines on the management of statin-associated myopathy, but these guidelines differ in many respects.[33,34] This is perhaps not surprising, considering that many of the recommendations are based on expert opinion, rather than on clinical trial data. The approach suggested in this article is based on review of the available guidelines, together with local experience at the Groote Schuur Hospital Lipid Clinic.

Measuring a baseline CK before the patient starts statins is useful as it alerts one to possible undiagnosed muscle disease, and provides a reference point against which further measurements can be compared. It is not necessary to routinely measure CK on follow-up in patients who tolerate statins well. In patients with muscle symptoms, the first, and often neglected, step is to confirm that the patient has a valid indication for statin therapy. Statin therapy may have been started without proper risk assessment, and the myopathy may be resolved simply by discontinuing the statin permanently.

Patients with a valid statin indication and muscle symptoms should have their CK measured. The location and severity of the muscle pain should be assessed. Other causes of musculoskeletal pain should be considered and appropriately evaluated. Table II lists selected causes of non-statin muscle pain.

Table II: Non-statin causes of musculoskeletal pain[30]

Unaccustomed physical exertion
Hypothyroidism
Fibromyalgia
Hyperthyroidism
Parathyroid disease
Cortisol excess or deficiency
Vitamin D deficiency
Viral illness, such as influenza
Polymyalgia rheumatica
Polymyositis
Neuromuscular disorders
Autoimmune disorders, e.g. systemic lupus erythematosus
Musculoskeletal disorders, e.g. bursitis and tendonitis
Drugs: corticosteroids, antiretrovirals, antipsychotics, colchicine and illicit drugs
Pyomyositis
Postictal state

It is important to specifically ask patients whether they have discontinued the statin themselves at any stage. Rapid symptomatic improvement on dechallenge, and recurrent symptoms with rechallenge, strongly support the diagnosis of statin myopathy. Patients with persistent symptoms several weeks after statin discontinuation are less likely to have statin myopathy, especially if there were pre-existent symptoms before statin initiation. Our experience is that the two most common, identifiable alternative diagnoses are hypothyroidism and fibromyalgia. If the thyroid-stimulating hormone has not been measured recently, then testing should be strongly considered as hypothyroidism is easy to miss. Patients with definite muscle weakness (not due to the patient withholding making a full effort due to pain) should proceed rapidly to a complete neuromuscular evaluation, as statin myopathy seldom causes definite weakness, and such patients often have undiagnosed neuromuscular disorders.[35]

If no alternative causes for the symptoms are identified, further management depends on the severity of symptoms and the CK. Patients with mild and tolerable symptoms, and a CK < 5 x ULN, can continue with the statin, but caution should be exercised when increasing the statin dose further. If the symptoms are severe, then statin discontinuation should be considered irrespective of the CK. The CK correlates poorly with symptoms, and patients may have disabling symptoms despite a normal CK. Statins are generally withheld until muscle symptoms have resolved. Once patients have recovered, alternative strategies can be considered (see below).

If CK elevation is found in asymptomatic patients, alternative explanations should be sought (see Table I). Unaccustomed or excessive exercise, e.g. weightlifting and horse riding, can elevate the CK markedly. The statin does not need to be discontinued if the elevated CK is readily explicable. Anecdotally, some patients who engage in very vigorous exercise report better performance and faster recovery if they discontinue the statin for a few days before and after a major sporting event, such as a marathon or triathlon. If the CK < 5 x ULN, the statin can be continued, but ongoing CK monitoring should be considered, especially if the statin dose is increased. Asymptomatic patients with an unexplained CK > 10 x ULN should temporarily discontinue the statin. Asymptomatic patients with a CK 5-10 x ULN should be monitored closely for a low threshold for dose reduction, or temporary discontinuation.

Alternative management strategies

Statins are the most effective low-density lipoprotein (LDL) cholesterol-lowering agents available, and their outcome benefit is well documented.[36,37] Therefore, this drug class should not be abandoned before alternative statin strategies have been tried. Patients need to understand that finding a suitable statin at a tolerable dose is often a process of trial and error. It is important to proceed systematically, with good documentation of symptoms and lipid responses.

There are three main alternative statin strategies that can be tried, either alone or in combination. The original statin can be prescribed at a reduced dose, an alternative statin can be prescribed (usually started at a lower effective dose than the previous statin), or non-daily dosing can be tried. If myopathy occurred when the dose of a previously well-tolerated statin was increased, down titration is often effective.

Statin-switching strategies have been tested in a limited number of studies, but trials with fluvastatin and rosuvastatin show that switching the statin can be successful in some patients with myopathy.[38,39] The new statin is generally started at a lower effective dose (a dose that will reduce the LDL cholesterol less). It can be difficult to determine whether it was the change in statin, or the dose reduction, that resulted in resolution of myopathy. Some medications (see Table I) interfere with statin metabolism, and a statin that does not interact with the patient's other medication, should be chosen.

Patients who cannot tolerate daily statin dosing may be prescribed statins on alternate days, or even as infrequently as once weekly. Non-daily dosing has been tried, mainly with atorvastatin and rosuvastatin due to their long half-lives.[40-43] Modest, but clinically useful LDL cholesterol reductions are achievable with non-daily dosing.

Using the strategies described above, it is usually possible to determine the maximum tolerable statin dose. If the LDL cholesterol remains unacceptably high, ezetimibe may be added to the statin.[44,45] Ezetimibe reduces cholesterol by inhibiting intestinal cholesterol absorption. Its mechanism of action is different from that of statins, and its use is infrequently associated with myopathy. Ezetimibe is only available as a fixed 10 mg daily dose, and adverse effects are uncommon.[46] Because ezetimibe is a relatively new drug, it still lacks cardiovascular outcome evidence.

Ezetimibe monotherapy is an option in patients who do not tolerate statins at all. Ezetimibe monotherapy reduces LDL cholesterol by about 18%, and it is often impossible to achieve complete LDL cholesterol control in patients who are completely intolerant to statins.[47] Bile acid sequestrants also lower LDL cholesterol. The only bile acid sequestrant available in South Africa is cholestyramine. Its utility is limited, as bloating and constipation are frequent adverse effects. Cholestyramine may also interfere with the absorption of other drugs.

Coenzyme Q10

Coenzyme Q10, or ubiquinone, is an end-product of mevalonate synthesis. Coenzyme Q10 is a component of the mitochondrial electron transport system, and therefore important for mitochondrial functioning. Statins inhibit mevalonate synthesis, and can potentially reduce coenzyme Q10 levels.[48,49] About 50% of coenzyme Q10 is thought to be endogenously synthesised, with the other 50% obtained from dietary uptake.[50]

Statins lower the serum levels of coenzyme Q10. This is mainly accounted for by the reduced LDL cholesterol associated with statin therapy, as LDL cholesterol is the major plasma carrier of coenzyme Q10. Whether statins reduce the intramuscular or mitochondrial levels of coenzyme Q10 is debatable. The majority of studies have found no association. Whether patients with statin myopathy have lower intramuscular coenzyme Q10 levels is also a matter of debate, as both positive and negative studies have been published. (Marcoff and Thompson[48] and Schaars and Stalenhoef[49] have reviewed the Q10 literature, if further reading is required).

The clinically more relevant question, namely whether supplementation with coenzyme Q10 will prevent statin myopathy or improve symptoms in those with myopathy, has unfortunately also not been definitively answered. Several small trials have been conducted. One trial compared coenzyme Q10 with vitamin E in 32 patients with statin myopathy. Pain scores decreased from baseline in the coenzyme Q10 arm, but remained unchanged in the vitamin E group.[51] Another study compared coenzyme Q10 to placebo in 44 patients with statin myopathy treated with simvastatin. There were no outcome differences (pain score or number of patients adhering to their statin treatments) between placebo and coenzyme Q10.[52] In yet another study, coenzyme Q10 was compared to placebo in patients on atorvastatin. In this study, muscle and liver enzyme values were the major end-points, and once again, no difference could be found between placebo and coenzyme Q10.[53] Several further studies of coenzyme Q10 are ongoing, and their results are awaited. Currently, the evidence that coenzyme Q10 is beneficial is inconclusive at best, and routine supplementation cannot be recommended. Coenzyme Q10 has no known adverse effects, except for the significant financial outlay required, and some patients report a symptomatic benefit. This is probably due to the placebo effect in many cases.

Red yeast rice

Red yeast rice is a popular, lipid-lowering dietary supplement that is freely available at most health stores. It is made by fermenting the yeast, *Monascus purpureus,* over rice, and has been used as a dietary supplement in China for centuries. This yeast secretes a family of substances called monacolins. One of the monacolins (monacolin K) is identical to lovastatin. Lovastatin production varies between different strains of the yeast, and the amount of lovastatin found in commercially available red yeast rice capsules is also highly variable.

Red yeast rice lowers LDL cholesterol,[54,55] and a partially purified red yeast rice extract (Xuezhikang) has been shown to reduce cardiovascular end-points in a Chinese post-infarction population.[56] Several small trials have investigated the use of red yeast rice in patients with statin myopathy.[57-59] Becker et al randomised 62 statin-intolerant patients to red yeast rice or placebo. LDL cholesterol was lowered by 0.90 mmol/l in the red yeast rice group, and by 0.39 mmol/l in the placebo group at week 24. Pain scores and CK did not differ between the groups.[57] In another study, red yeast rice was compared with pravastatin 20 mg, twice daily, in 43 statin-intolerant patients. LDL cholesterol reductions, pain scores and CK measurements did not differ between the two groups.[58]

However, red yeast rice should be regarded as a medication, and not a dietary supplement. It is neither free of adverse effects, nor perfectly safe. Myopathy, including rhabdomyolysis, can occur in red yeast rice users,[60,61] and hepatitis has also been described.[62] As red yeast rice production is largely unregulated, concentrations of the active ingredients can vary markedly among different commercial preparations. Some preparations also contain citrinin, which is a nephrotoxin.[63] Ideally, red yeast rice production needs to be standardised and regulated, followed by adequately powered safety and efficacy trials. Patients who want to take red yeast rice preparations should be informed that currently, red yeast rice is not adequately regulated or standardised. Although red yeast rice can be obtained without a prescription, it may still cause adverse effects.

Hepatotoxicity

Statins are regarded as "hepatotoxic" by many doctors and patients. Such concerns are often unfounded and excessive, and may at times even cause doctors to withhold statins when they are indicated, and their use would be entirely safe.[64,65] Statins may cause mild elevations in alanine aminotransferase (ALT) in up to 10% of recipients, and in 1-3% of patients, the ALT may be more than 3 x ULN.[66] This transaminitis is often seen in the first three months of therapy. However, such ALT elevations do not translate into clinical liver disease or liver failure.[67] The rate of acute liver failure in statin users is not higher than the background population rate.[68] This does not mean that statins never cause liver injury. There are definitely cases in which liver injury was most probably due to statin therapy.[69] However, these cases are extremely rare, and statins should not be regarded as more hepatotoxic than most other commonly used drugs.

Abnormal liver function tests in patients taking statins are often ascribed to the statin. This approach may do more harm than the statin itself, as it may lead to a failure to investigate and identify potentially treatable causes. Persistent liver function abnormalities in patients on statins should be investigated in the same way as in patients on no medication. If the ALT > 3 x ULN, the statin should be temporarily discontinued, and investigations into other causes of transaminitis requested. The patient can then be rechallenged with statins once the ALT has normalised. Liver function tests should be monitored following rechallenge to ensure continued normalisation.

Patients with elevated transaminases measured at baseline often pose a management dilemma, with physicians concerned about the risk of exacerbating the liver disease. Elevated baseline liver function tests are not uncommon in clinical practice, as many patients at high cardiovascular risk have other disorders such as non-alcoholic fatty liver disease, chronic viral hepatitis and iron overload. These patients are often denied statins for fear of worsening their hepatic disease. Patients with persistently elevated liver function tests should be investigated to identify the underlying cause of liver disease, and its severity. If the liver disease is stable and compensated carefully, supervised statin therapy can be initiated. This recommendation is discordant with the approved label (package insert) of most statins, which contraindicates their use in chronic liver disease. However, an expert panel of hepatologists recently reviewed all available statin safety data, and concluded that stable chronic liver disease and compensated cirrhosis are not contraindications to statin therapy.[70] Subsequently, this approach has been supported by many other authors.[64,69,71-74]

Whether, when and how often liver function tests should be monitored in patients on statins is controversial. The National Cholesterol Education Panel guidelines recommend baseline testing, a test at 12 weeks, and then annual monitoring.[75] However, the clinical value of such an approach is questionable, as there is no evidence that routine monitoring identifies patients at risk of serious toxicity. Statins have an excellent hepatic safety record, and in many studies, persistently elevated liver enzymes have turned out to be false positives.[76] Baseline testing makes sense as it provides a reference for future comparison, and may lead to the identification of undiagnosed liver disease. Further monitoring should be individualised.[33]

Conclusion

Statins have an excellent and well-established safety record. In clinical practice, myopathy is the most bothersome side-effect, but this problem can be resolved or ameliorated in many patients. However, there is a small group of patients who remain completely intolerant to statins. These patients have limited treatment options, including ezetimibe and

cholestyramine, and their LDL cholesterol often cannot be well controlled. Statins are not particularly hepatotoxic drugs, and hepatic adverse events that preclude statin prescription are very rare. Statins may occasionally cause other adverse effects, e.g. simvastatin may cause headaches in some patients, which has not been discussed in this article. These other adverse effects are not likely to be class-related, and a statin switch will often solve the problem.

When dealing with patients on statins, clinicians often tends to focus on those who report adverse effects. Just as important, if not more important, are those patients who have quietly stopped taking their statins. Patients will often not inform their doctor that they have stopped the statin, and may even continue coming in for prescriptions that they never fill. Lipid management does not end when the first prescription has been written, but requires regular follow-up with monitoring of lipids (adequacy of treatment, adherence and persistence) and direct questions about adherence and persistence. Ensuring adherence and persistence is often a greater clinical challenge than dealing with the adverse effects.

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