Statin therapy and liver dysfunction: a challenging case history

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Should statin therapy be continued if liver function blood tests on a scheduled review indicate increased levels of transaminases?

Key points

- **Statins remain a standard part of cardiovascular therapy.**
- **Follow-up blood testing of lipids and liver and muscle enzymes still has a role as part of general monitoring. It should be performed at yearly intervals or even more frequently.**
- **Statin therapy may occasionally cause severe liver dysfunction, usually manifesting as rises in the levels of the transaminases (ALT, AST). Minor increases in the transaminases occur more frequently, due to a variety of nonspecific reasons.**
- **In the presence of a minor increase in transaminases and an otherwise uncomplicated history, it is reasonable to continue statin therapy unchanged and monitor the progress over the next four to six weeks. By that time minor increases have usually resolved.**
- **Unfortunately, patients may experience a further coronary event despite good adherence to the best care available.**

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Case scenario

Mr BC is 64 years old and has a three-year history of angina. Cardiac investigation revealed that revascularisation was not required at the time of original presentation. He has stopped smoking, his body weight and his blood pressure and glucose levels have been satisfactory, and he continues with his usual drugs (nitrate, aspirin, beta blocker and ACE inhibitor). He is taking atorvastatin 80 mg daily for cholesterol control. He feels generally well.

He attends his GP for a scheduled review. Follow-up blood test results are shown in the Table.

How do we interpret these findings?

Mr BC's lipid profile one year ago was satisfactory for a high-risk patient and remains so, with his LDL cholesterol level at or below 2.0 mmol/L. His triglycerides are acceptable, given the satisfactory HDL cholesterol readings. The creatine kinase level is unremarkable and he has no muscle symptoms. His liver enzymes were unremarkable a year ago but the transaminases (alanine transaminase [ALT] and aspartate transaminase [AST]) are now significantly higher. His statin dose is at the maximum recommended for atorvastatin, but this dose is often used in patients with established coronary heart disease.

Table. The patient's blood test results

Results	Total cholesterol (mmol/L)	LDL cholesterol (mmol/L)	HDL cholesterol (mmol/L)	Triglycerides (mmol/L	Creatinine (µmol/L)	Glucose (mmol/L)	CK (U/L)	ALT (U/L)	AST (U/L)	GGT (U/L)
One year ago (on treatment)	3.8	1.7	1.2	2.0	74	4.8	202	32	28	52
Today, at scheduled review (on treatment)	4.0	2.0	1.1	1.9	78	4.9	185	80	46	60

ABBREVIATIONS: ALT = alanine transaminase; AST = aspartate transaminase; CK = creatine kinase; GGT = gamma glutamyl transferase; HDL = high density lipoprotein; LDL = low density lipoprotein.
Selected reference values: Creatinine <110 µmol/L; glucose <5.5 mmol/L; CK <230 U/L; ALT and AST <45 U/L; GGT <55 U/L.

Although statins may occasionally cause severe liver dysfunction, usually manifest as rises in the transaminases rather than in the gamma glutamyl transferase (GGT), minor increases in transaminases occur more frequently. These minor increases are due to various nonspecific reasons. Other diagnoses, such as viral disease, excess alcohol intake or fatty liver, seem less likely in this patient, given the history and modest enzyme changes. His other medications are unlikely to be relevant here.

How should these findings be managed?

If Mr BC's ALT level had increased to more than three times the upper reference level, and in knowledge of his earlier favourable ALT levels, his statin therapy would need to be stopped. As it is, the increase in Mr BC's ALT level is more marginal, but some doctors would still stop his statin therapy. Either of these scenarios would create a potential treatment void that would be difficult to manage.

The author's preferred approach here is actually *to do nothing* and await developments over the next four to six weeks. This was also the advice of Mr BC's GP, and when reassessed six weeks later, Mr BC's liver enzymes were more favourable (ALT, 41 U/L; AST, 31 U/L; and GGT, 50 U/L). This favourable situation then persisted.

Implications for patient management

There is an emerging school of thought suggesting that, in a patient on statin therapy, there is less need to monitor liver enzymes on a regular basis after initial follow up at, say, six to eight weeks. This is based on the low incidence of subsequent liver dysfunction in such patients that has been shown in placebo-controlled trials. Hence, this whole scenario might have been avoided by not doing blood tests. However, it is the author's view that these trials underestimate the true incidence of liver dysfunction, largely because of the narrow inclusion criteria of clinical trials.

The author is still in favour of some long-term blood testing, say at yearly intervals (or even more frequently). Such testing may also provide further motivation for patients to persist with long-term therapy in settings where poor compliance is likely to be a major challenge. In retrospect, this patient had real changes in transaminase levels but these were probably unrelated to his therapy.

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Case scenario continued

Mr BC is now 67 years old, and his angina was diagnosed over six years ago. Since his presentation to his GP three years ago for a scheduled review, he has continued not smoking and to use the standard cardiovascular medications to reduce his coronary risk. His mild liver dysfunction has not been a problem, his lipid therapy has continued unchanged and he has been very compliant. In fact, he had remained very well.

Eight weeks ago, however, he suffered a myocardial infarction. He is now upset that this occurred despite all the treatment he has taken over the years.

Why did this happen?

Some patients (and even a few doctors) have the erroneous view that modern preventive therapy will eliminate future cardiovascular risk. Controlled trials with statins demonstrate a significant reduction in relative risk of a future event of about 30% over five years, and there is probably a greater improvement with multiple interventions over many more years. Nevertheless, the biggest challenge in modern cardiology today remains a relatively high level of residual risk, despite our best interventions.

Conclusion

This case illustrates that although statin therapy may be associated with liver dysfunction, minor increases in a patient's transaminase levels are usually due to nonspecific causes rather than to statin therapy. In the presence of a minor increase in transaminases and an otherwise uncomplicated history, it is reasonable to continue statin therapy unchanged and monitor the progress over the next four to six weeks, by which time the minor increases have usually resolved.

Unfortunately, patients may experience recurrent coronary events despite good adherence to the best care available. **CT**

COMPETING INTERESTS: None. The views expressed are purely those of the author.