Statin therapy: could liver function monitoring be reduced

An inner East London clinical commissioning group introduced local guidance on when to test liver function in people on statins using a single enzyme liver function test (LFT) in line with the NICE guideline on cardiovascular disease, rather than a full set of LFTs. An observational study suggested that this reduced the frequency of LFT requests in this group, may reduce the associated costs and reduces inappropriate decision making, such as unnecessarily discontinuing statin therapy. The NICE guideline recommends using a single enzyme LFT at baseline, within 3 months of starting a statin, and at 12 months, but not again unless clinically indicated. However, the ability for GPs to select single enzyme LFTs is limited in some localities in the UK.

Overview and current advice

There have been long-standing concerns about liver toxicity associated with statin use, however more than 30 years of experience of using statins in practice suggests that they do not cause liver disease\(^1\).

The summaries of product characteristics for the various statins state that they can cause an increase in liver transaminases. In most cases these increases are mild or moderate and transient in nature. The NICE guideline on cardiovascular disease: risk assessment and reduction, including lipid modification recommends that statin therapy should not be routinely excluded in people who have liver transaminase levels that are raised but less than 3 times the upper limit of normal.

Routine annual monitoring of liver function for people on statins is not recommended by NICE. The NICE guideline on cardiovascular disease recommends that liver transaminase enzymes (alanine aminotransferase [ALT] or aspartate aminotransferase [AST]) are measured:

- before starting a statin,
- within 3 months of starting a statin, and
- at 12 months, but not again unless clinically indicated.

In the UK, single enzyme liver function tests (LFTs) such as ALT and AST are not routinely available for GPs to select when ordering LFTs. This means that people on statins are often monitored using a full LFT which can include up to 7 different parameters. In addition, uncertainty over the need for periodic LFTs for people on statins can lead to unnecessary over testing\(^1\).
New evidence

An observational study1 investigated the effect of an intervention to reduce liver function monitoring ordered by GPs for people on statin therapy.

Two neighbouring inner East London clinical commissioning groups (CCGs; Tower Hamlets and Newham) with 95 general practices serving a population of 650,000 people were included. Tower Hamlets was the intervention CCG and Newham was included as a control CCG for comparison. Data were taken from GP practice electronic health records.

The intervention consisted of allowing GPs to select a single enzyme (ALT) test to check liver function in people on statins (rather than full LFTs), and the introduction of locally developed guidance on frequency of testing from April 2015. The guidance recommended a single ALT test before starting statin treatment but no further testing unless clinically indicated. It was amended in October 2015 to allow for a single repeat ALT test after 3 months for people on high-intensity statins in line with NICE Quality Standard 8 in Cardiovascular risk assessment and lipid modification. The guidance was sent electronically with paper copies to all GPs in Tower Hamlets and was promoted at 2 educational meetings. Neither the guidance nor the single enzyme test was available in Newham.

In the total population of the 2 CCGs, 62,285/353,001 people (17.6%) were on statins at baseline. These accounted for 43.2% (15,793/36,540) of all full LFTs requested before the intervention. A total of 2.5% of the population had liver disease and these accounted for 5.1% (1,847/36,540) of the total LFTs requested.

In Tower Hamlets, there was a statistically significant reduction in the average rate of full LFTs from 70.3/1000 people on statins (95% confidence interval [CI] 66.3 to 74.6) in the pre-intervention year to an average of 58.1/1000 (95% CI 55.5 to 60.7) in the post-intervention year (p<0.001). The rate of full LFTs per 1000 people on statins in the last month of the post intervention year (March 2016) was 53.2, representing around a 25% reduction on the average pre-intervention rate.

In Newham, there was no statistically significant reduction in the rate of full LFTs for people on statins. The average rate was 96.3/1000 (95% CI 90.5 to 102.1) in the pre-intervention year and 93.0/1000 (95% CI 88.6 to 97.3) in the post-intervention year (p=0.32). The rate per 1000 people in the last month (March 2016) was 90.6, representing a reduction of 5.9% on the average pre-intervention rate.

In Tower Hamlets, the cost of a full LFT was priced at £45.50 and a single ALT test was £6.50. Taking into account the reduction in full LFTs, and offsetting the cost of the additional single ALT tests, the authors estimated a saving of £130,435 on liver function testing for people on statins post intervention compared with the pre-intervention year.

The study had limitations. It only included LFTs requested by GPs and did not include those requested by hospital clinicians, therefore the potential gains may have been underestimated. In addition, the 2 CCGs studied were not representative of an average CCG in the UK. The included populations were economically deprived and ethnically diverse with high levels of cardiovascular disease, diabetes and statin use. Nevertheless, the authors suggest that the problem of unnecessary LFTs is likely to be relevant to all areas in the UK.

Commentary

Commentary provided by Professor Anthony Wierzbicki, Consultant in Metabolic Medicine and Chemical Pathology, Guy's & St Thomas' Hospitals, London, UK
The basis of LFT monitoring for any drug is the application of Hy's law, which is a measure of acute liver injury expressed as serum bilirubin more than 2 times the upper limit of normal (ULN) and ALT more than 3 times the ULN, with no other causes. These criteria, if met, are associated with a more than 10% risk of mortality due to acute liver failure. In practice, bilirubin elevations occur only in extreme cases and raised liver transaminases alone may not be of clinical significance. Routine practice for hepatocellular toxicity is to advise discontinuation of a statin if ALT (or AST) is more than 3 times the ULN on repeated testing. The ULN is an arbitrary cut-off relying on population background rates of liver dysfunction to establish a reference range. Epidemiological studies of hepatic dysfunction suggest that normal ALT is about 19–25 IU/L in females and 29–33 IU/L in males, and levels higher than these are associated with increased risk of liver disease. Most UK reference ranges use 45–55 IU/L as typical ULNs.

Studies of statin toxicity show that these medicines can cause increases in transaminases (often in a dose-dependent manner) but that liver injury is rare. In most cases, increases in transaminases are mild or moderate and transient in nature, and virtually all transaminase elevations resolve with decreased doses or discontinuation. Therefore, guideline committees in the US and Europe now suggest less frequent monitoring than in the past. The NICE guideline on cardiovascular disease: risk assessment and reduction, including lipid modification recommends baseline, 3-month and 12-month transaminase tests, but then not again unless clinically indicated for all people on statins.

There is no consensus on the components to be included in a full LFT panel. Commonly they include bilirubin and one or more transaminases (AST or ALT) and alkaline phosphatase. Unbundling panels is straightforward but depends on the flexibility of computerised primary care ordering systems. Most LFT panels cost £5–10. The fixed costs of phlebotomy, transport and laboratory analysis comprise 90–95% of costs. The cost savings for abbreviated panels are mostly caused by a reduction in consumables (£0.06–0.50 per analyte depending on costing models) and an increased analyser throughput. The most important effect clinically is to reduce inappropriate decision making. There is a common misapprehension that any LFT disturbance means that statin therapy should be discontinued or not started. The result is that patients are subject to repeated visits, increased anxiety and may inappropriately discontinue statins, potentially meaning they are at increased risk of cardiovascular disease. Therefore, monitoring single LFTs, such as ALT alone, could improve logistics, reduce anxiety and aid appropriate care by concentrating on the most relevant biomarker of drug-induced hepatic dysfunction.

Declaration of interests:
Professor Anthony Wierzbicki has received expenses from the PCSK9 Forum; sat on the international steering committee for the STAREE trial; and been the site clinical lead investigator for trials of lipid-lowering drugs for Amgen, Merck Sharp & Dohme and Akcea and the clinical registry lead for Chiesi.

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References

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