Technology Assessment Report commissioned by the NIHR HTA Programme on behalf of the National Institute for Health and Clinical Excellence.

Project 09/16

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1. Title: Insulin sensitizers in treatment of non-alcoholic fatty liver disease

2. Aberdeen TAR team

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3. Plain English Summary

Non-alcoholic fatty liver disease (NAFLD) is a common disease due to a build up of fat in the cells of the liver. It can range from causing no symptoms at all, to severe damage (cirrhosis) of the liver, and death. Liver disease is common in those who drink to excess, but liver disease can also occur in people who drink little or no alcohol (defined as less than one unit, 10g, a day), especially if they are fat.

NAFLD is becoming more common because of the rise in obesity, and it is estimated that about 20% of people in the USA have it. It is also the most common cause of liver disease in children.

In the early stages of NAFLD, the liver is simply full of fat (steatosis), but this can progress to inflammation (steatohepatitis), and then to scarring and cirrhosis. It used to be seen typically in middle age, but with increasing levels of obesity in children, cases have been reported in children under 10.

Most people who get NAFLD are overweight or obese, and there is a close association with insulin resistance. More than half of the people with NAFLD will also have type 2 diabetes, and many will have high cholesterol levels. There is an increased risk of heart disease.

Treatment should start with diet and weight loss, aided by physical activity, and if sufficient weight is lost, the condition will improve. However adherence to lifestyle changes is often poor.

Because NAFLD is usually seen in people who have insulin resistance, a group of drugs which improve the body's sensitivity to insulin have been tried. These drugs are called the insulin sensitisers - metformin, pioglitazone and rosiglitazone.

This review will examine the evidence for the effectiveness of these drugs in NAFLD.

4. Decision problem

- Key question: what is the clinical and cost-effectiveness of metformin, rosiglitazone and pioglitazone in NAFLD?

- Should the HTA Programme seek to commission further primary research in the value of insulin-sensitisers in NAFLD?

It will be assumed that first-line treatment will be with lifestyle changes (diet, physical activity and weight loss), and that the insulin-sensitisers will be used as a second-line addition to those. A Cochrane review on dietary interventions by Rex Wang and colleagues is in progress, and we will not examine the literature on that.

Given recent evidence on the relative vascular risks of pioglitazone and rosiglitazone (summarised in the HTA monograph on newer drugs for type 2 diabetes), our prior position will be that pioglitazone is preferred. We will exclude any studies which used troglitazone, an earlier glitazone which is no longer used because it caused liver damage.

The population of interest will be those with diagnosed NAFLD, and the HTA Programme commissioning brief specifies that the patient group of most interest is people with evidence of fibrosis.

Sub-groups will include;

- Those with type 2 diabetes
- Children and adolescents
- Those with other features of the metabolic syndrome such as hypertension and hyperlipidaemia.
- Those with and without fibrosis
- Ethnic groups at higher risk

Diagnosis

There is a problem with the diagnosis of NAFLD. The current consensus is that it can only be diagnosed on the basis of a liver biopsy. This could be a major hindrance to any trials which need to recruit large numbers of patients, perhaps especially if young people are involved. Liver biopsy can have complications, such as bleeding, at any age.

Hence it would not be feasible to mount a large trial of insulin-sensitisers if the diagnosis has to be based on liver biopsy. We are aware that research into alternative methods of diagnosis, such as panels of liver tests, ultrasound and MRI, is underway.

For detecting NAFLD, ultrasound and MRI have been suggested. For detecting liver fibrosis, various non-invasive alternatives to liver biopsy have been suggested, including combinations of blood tests (“serum marker panels”), and either transient or real-time elastography.

The HTA Programme is commissioning a full review of evidence on non-invasive methods for the assessment and monitoring of more advanced stages, liver fibrosis and cirrhosis (HTA number 09/07), and so this review will not duplicate that. This review is more concerned with a trial which would seek to prevent people reaching those stages.

The aim for diagnosis is therefore to distinguish those patients with simple steatosis from those who have steatohepatitis.

We will therefore carry out a brief review of alternatives to biopsy at earlier stages, such as NASH.

What we will try to do is identify non-invasive tests which could be used to recruit patients to a trial, even if that meant accepting that the tests were sensitive but not specific. The safety and adverse effects of the drugs under review are well-known and that the drugs are well tolerated and safe. Hence a case could be made that using a test which had good sensitivity but not very good specificity, would be suitable for identifying patients for a trial, on the grounds that including some people who had fatty livers but had not progressed to NASH, would do them no harm, but possibly some good.
However it might reduce the power of the study by reducing the frequency of adverse outcomes in the placebo arms.

Our aim will not be to make a firm recommendation as to what diagnostic tests should be used in a trial, but rather to suggest non-invasive options which the HTA Programme could include in the vignette and then the CB. It would then be up to bidders to justify their choices.

5. Report methods for synthesis of evidence of clinical effectiveness

A review of the evidence for clinical effectiveness will be undertaken systematically following the general principles recommended in NHS CRD Report No.4.

Criteria for considering studies for this review

Types of studies: systematic reviews and randomised clinical trials. There will be no size restriction on number of patients in trials, since those with inadequate numbers and hence power, might be useful when combined in a meta-analysis. Observational studies may be used for data on safety and for assessing diagnostic methods.
We note the Cochrane review on insulin sensitisers by Francesco Angelico and colleagues in Rome. It excluded people with type 2 diabetes, and only included three trials, two of metformin and one with pioglitazone. Our scoping searches suggest that there may be another nine trials which need to be considered.

Types of participants: Participants of any age, sex, or ethnic origin with NAFLD proven by liver biopsy or other methods.

Types of interventions: Metformin, pioglitazone, or rosiglitazone at any dose or duration, given separately or in combination versus no intervention, placebo, or other pharmacological interventions of proven effectiveness.

Types of outcome measures: Measures of disease progression such as fibrosis and cirrhosis, other hepatic-related morbidity such as variceal bleeding liver failure, hepatic-related and all-cause mortality, cardiovascular events, quality of life, new diabetes, adverse events. We include some of these for completeness but do not expect studies to be large enough or long enough to report on all of these outcomes.

We will check the diagnostic methods used in previous trials, and if data permit, we will compare the findings of liver biopsy with those of non-invasive tests. We will

carry out searches on diagnostic methods other than liver biopsy. Ideally, these would compare new tests with liver biopsy as the gold standard.

Search methods for identification of studies

We will search the following sources

- MEDLINE
- EMBASE
- The Cochrane Library (all sections)
- Science Citation Index Expanded (SCI expanded) and Conference Proceedings Citation Index- Science (CPCI-S)
- Contact with experts in the field
- Scrutiny of bibliographies of retrieved papers

We will search for articles published since 2005, since a Cochrane review included studies found by searches to February 2006. No language restrictions will be applied to the search strategy, but we may not be able to translate studies in languages other than English, German and French.

Data collection and analysis

Study Selection: Study selection will be made independently by two reviewers. Discrepancies will be resolved by discussion, with involvement of a third reviewer when necessary.

Data extraction: Data will be extracted by one reviewer, using a standardised data extraction form, and checked by a second. Discrepancies will be resolved by discussion, with involvement of a third reviewer when necessary.

The quality of the individual studies will be assessed by one reviewer, and independently checked for agreement by a second reviewer. Any disagreements will be resolved by consensus and if necessary a third reviewer will be consulted. The quality of the clinical effectiveness studies will be assessed according to criteria based on NHS CRD Report No.4.

Existing systematic reviews will be quality assessed, summarised and results compared. Reasons for differences between the reviews will be investigated and possible reasons for conflicting results will be investigated in a narrative review.

RCTs published since the existing systematic reviews will be added and included if appropriate in a new meta-analysis. If not, evidence synthesis of all RCTs which meet our inclusion criteria will be done using a narrative review.

Searches will be carried out for on-going research.

We will contact the authors of the Cochrane review and if they are updating it in our timescale, will offer collaboration. If they are not doing it in our timescale, we will invite them to act as peer reviewers of the unpublished draft final report.

6. Report methods for synthesising evidence of cost-effectiveness

We will review the literature on cost-effectiveness but will not undertake any de novo modelling.

7. Products

The main product from this review will be a short report for publication in the HTA monograph series, but as requested in the commissioning brief, we will also produce a vignette on the desirability of new primary research for the Pharmaceutical Panel of the HTA Programme. We will also aim to submit a version suitable for publication in an appropriate journal. We will contact the authors of the Cochrane review with a view to helping them update their review.

8. Competing interests of authors

None.

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An expert in liver disease is being approached to join the team.

Timetable/milestones
Assessment Report to be delivered by end July 2010