

A systematic review and economic evaluation of cilostazol, naftidrofuryl oxalate, pentoxifylline and inositol nicotinate for the treatment of intermittent claudication in people with peripheral arterial disease

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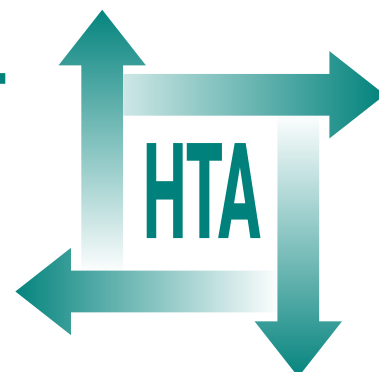
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Executive summary

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Executive summary

Background

Peripheral arterial disease (PAD) is a condition in which there is blockage or narrowing of the arteries that carry blood to the legs and arms. It is estimated to affect around 4.5% of people between the age of 55 and 74 years within the UK. The most common symptom of PAD is intermittent claudication (IC), characterised by pain in the legs on walking that is relieved with rest. The treatment of IC is targeted at reducing the risk from cardiovascular events and includes smoking cessation, cholesterol lowering, glycaemic control, weight reduction and blood pressure control. Symptoms can be managed with exercise therapy and/or pharmacological therapies, including cilostazol (Pletal[®], Otsuka Pharmaceuticals), naftidrofuryl oxalate (Praxilene[®], Merk Serono), pentoxifylline (Trental 400[®], Sanofi-aventis) and inositol nicotinate (Hexopal[®], Genus Pharmaceuticals).

Objectives

To assess the effectiveness and cost-effectiveness of the following vasoactive drugs for IC due to PAD in adults whose symptoms continue despite a period of conservative management:

- cilostazol
- naftidrofuryl oxalate
- pentoxifylline
- inositol nicotinate.

Methods

A systematic literature review was conducted of the clinical effectiveness and cost-effectiveness of cilostazol, naftidrofuryl oxalate, pentoxifylline and inositol nicotinate within their licensed indications for the treatment of IC in people with PAD whose symptoms continue despite a period of conservative management. Electronic bibliographic databases were searched during April to June 2010 (MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, The Cochrane Library databases, Cumulative Index to Nursing and Allied Health Literature, Web of Science, Conference Proceedings Citation Index, BIOSIS Previews). The reference lists of relevant articles were also checked. Comparators were placebo, usual care of PAD without the vasoactive drugs assessed within this report and the vasoactive drugs for PAD compared with each other. Outcomes sought were maximal walking distance (MWD), pain-free walking distance (PFWD), ankle-brachial pressure index, cardiovascular events, mortality, adverse events (AEs) and health-related quality of life (HRQoL). A narrative synthesis was provided for all outcomes and a network meta-analysis was also undertaken for the MWD and PFWD outcomes.

A Markov model was developed to assess the cost-effectiveness of each vasoactive drug for PAD compared with no vasoactive drugs and with each other vasoactive drug from a NHS and PSS perspective. The model has three states: vasoactive drug treatment, no vasoactive drug treatment and death. Patients will start with one of the drugs under evaluation and after each weekly cycle may continue with the drug, discontinue with the drug or die. Patients may also start with no

drug treatment. The time horizon of the model is the lifetime of the patients. Regression analysis was undertaken to model the relationship between MWD and utility so that a cost per quality-adjusted life-year (QALY) outcome measure could be presented. Given the uncertainties around the quality-of-life evidence and the uncertain long-term outcomes, a threshold analysis was also undertaken. There was only one manufacturer submission (Otsuka) for this assessment and no economic model was provided.

Results

Twenty-six randomised controlled trials (RCTs) were identified that met the inclusion criteria for the clinical effectiveness review. These included trials comparing each of the vasoactive drugs for PAD with placebo, and also head-to-head comparisons of cilostazol and pentoxifylline, and cilostazol with usual care.

There was evidence to suggest that walking distance outcomes were statistically significantly improved by both cilostazol and naftidrofuryl oxalate; the 95% credible intervals for the difference from placebo in the logarithm mean change from baseline were 0.108 to 0.337 and 0.181 to 0.762, respectively. It was not possible to include inositol nicotinate within the meta-analysis of MWD and PFWD because of the lack of 24-week data. AEs were minor for all drugs and included headaches and gastrointestinal difficulties. The incidence of serious adverse events (SAEs), including cardiovascular events and mortality, was not increased by the vasoactive drugs compared with placebo. However, most studies had a relatively short follow-up time to address this outcome. HRQoL data are limited, as outcomes were often partially reported, not reported or not measured. There is some evidence that cilostazol improves physical function but does not affect mental health or overall quality of life. There are very limited data for naftidrofuryl oxalate and pentoxifylline. Naftidrofuryl oxalate may improve daily living, social life and mood, but not anxiety, and pentoxifylline has little effect on HRQoL. There was no HRQoL evidence for inositol nicotinate. Patient-level Short Form questionnaire-36 items HRQoL data were obtained from one RCT and these data were used within the economic evaluation.

The economic evaluation suggests that naftidrofuryl oxalate dominates cilostazol and pentoxifylline, and has an incremental cost per QALY gained of around £6070 compared with no vasoactive drug. This result is reasonably robust to changes within the key model assumptions. The exception to this is the results of an exploratory subgroup analysis of patients with more severe IC, in whom successful vasoactive drug treatment may prevent the need for angioplasty. This is predicted to result in an incremental cost per QALY gained below £20,000 for no vasoactive drugs (all patients receive angioplasty) versus the vasoactive drugs. However, the assumptions within this subgroup analysis are largely based upon clinical advice owing to lack of evidence. This analysis is therefore highly uncertain, meaning that these results should be treated with caution. It was not possible to include inositol nicotinate within the base-case analysis owing to lack of 24-week data; however, because of its higher acquisition cost it would have to demonstrate considerably greater impacts upon quality of life than the other vasoactive drugs being assessed for it to have a cost per QALY gained below £20,000 compared with no vasoactive drug, and this is not suggested from the 12-week data.

Discussion

The main strengths of the review are that the literature search was comprehensive and that the included studies were of relevance to UK practice in terms of populations. In addition, all included trials prescribed medications in line with UK marketing authorisations. However, most

of the trial data had follow-up periods of 24 weeks, which is relatively short term compared with clinical practice.

Within the meta-analysis of MWD and PFWD, several studies were excluded because the published reports did not provide data in a form that was suitable for inclusion in the meta-analysis. In the analysis, it was assumed that the data from the studies were missing at random and that the lack of usable data was not related to the observed treatment effect.

There is much uncertainty regarding the change in utility and discontinuation rate beyond 24 weeks because most RCTs do not have follow-up beyond this time point. Any additional effectiveness of naftidrofuryl oxalate beyond discontinuation would improve cost-effectiveness, and a sensitivity analysis was carried out to test alternative long-term discontinuation rates which did not have a substantial impact upon the results.

The regression model fitted to predict the change of utility from the change of MWD within the health economic model was based on patient-level data from a RCT of cilostazol of 106 patients in the UK. The underlying assumption of this analysis is that there is the same relationship for all drugs and no vasoactive drug between MWD and utilities. Direct long-term utility data associated with each of the drugs would provide less uncertain estimates of cost-effectiveness. A threshold analysis was undertaken to address this issue. A value-of-information analysis has not been undertaken because of the uncertainties associated with the long-term outcomes, which it was not possible to fully quantitate within the probabilistic sensitivity analysis.

Cardiovascular AEs are common for the patient population considered in the study. The long-term safety of cilostazol was tested in a good-quality trial, which suggests that there is very little difference between cardiovascular outcomes for cilostazol and placebo, and personal communication with the team of clinical advisors suggests that there is no clinical reason why these vasoactive drugs for PAD would impact upon the number of cardiovascular events. However, there are no long-term safety studies on naftidrofuryl oxalate, pentoxifylline or inositol nicotinate, and if there was a small increase or reduction in the incidence of cardiovascular events when patients are on these drugs then the cost-effectiveness results could alter substantially because of the otherwise small impact on costs and quality of life associated with these drugs.

Conclusions

Naftidrofuryl oxalate and cilostazol are both effective treatments for this patient population, with minimal SAEs; however, naftidrofuryl oxalate is the only treatment with an incremental cost per QALY gained below £20,000 compared with no vasoactive drug. There is, however, uncertainty regarding long-term effectiveness, and hence a trial comparing the long-term effectiveness (beyond 24 weeks) of cilostazol, naftidrofuryl oxalate and placebo would be beneficial, which should collect utility data as well as walking distance outcomes. It would also be useful to compare the outcomes associated with naftidrofuryl oxalate with those associated with supervised exercise programmes and other treatments, such as angioplasty. Importantly, there are currently no long-term safety trials for naftidrofuryl oxalate; however, clinical experts suggest that the mechanism of the drugs is such that no long-term impacts on cardiovascular events or mortality would be expected.

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Publication

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NIHR Health Technology Assessment programme

The Health Technology Assessment (HTA) programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

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