Centre for Reviews and Dissemination

NHS
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Evidence briefing on drug treatments for functional class II pulmonary hypertension

- The North of England Specialised Commissioning Group is the lead organisation charged with commissioning targeted therapies for adults with pulmonary hypertension in England.
- Targeted therapies are currently commissioned for adults with functional class III pulmonary hypertension (marked limitation of physical activity) but not for those in class II (slight limitation on physical activity).
- European Society of Cardiology guidelines recommend three drugs (ambrisentan, bosentan and sildenafil) as first-line therapies for patients with functional class II pulmonary hypertension. It is unclear from the guidelines how the available research evidence has been used to inform these recommendations.
- The Scottish Medicines Consortium (SMC) has also approved ambrisentan and sildenafil for patients in this group.
- There are currently some 80 patients with functional class II PAH being treated at specialist centres in England. Commissioning treatment for these patients with sildenafil would incur costs of at least £500,000 per year. It is likely that there are patients outside the specialist treatment centres who would present for treatment if available but the number of patients involved is uncertain.
- We identified six systematic reviews of drug therapies for pulmonary hypertension but none of these focuses specifically on patients in functional class II. The most up-to-date systematic review included 24 double-blind, placebo-controlled randomised trials. Only one of these recruited exclusively patients in functional class II. Five other randomised trials included between 30% and 50% of patients in functional class II, the remainder of participants being mainly in class III.
- We found no fully published economic evaluations of drug therapies for functional class II hypertension.
- Limited details of manufacturers' submissions to the SMC are available, which makes it difficult to evaluate the strength of the cost-effectiveness evidence supplied by the manufacturers.
- Overall, few patients with functional class II disease have been included in randomised trials. Based on the published results of trials included in the most up-to-date systematic review, there is no clear evidence of benefit for any of the three dugs recommended by the ESC guidelines when compared to placebo in patients with functional class II disease.

This evidence briefing has been produced for the North of England Specialised Commissioning Group by the Centre for Reviews and Dissemination (CRD). Full details of methods are available on request (paul.wilson@york.ac.uk or duncan.chambers@york.ac.uk).

CRD is part of the National Institute for Health Research (NIHR) and a department of the University of York. The Centre produces and disseminates systematic reviews and associated economic analyses that evaluate the effects of health and social care interventions, and the delivery and organisation of health care. www.york.ac.uk/inst/crd.

Background

Pulmonary hypertension (PH) is a rare disorder characterised by raised pressure in the pulmonary artery. It can be associated with a range of clinical conditions but the most common type is pulmonary arterial hypertension (PAH), defined as a clinical condition with the presence of pre-capillary PH in the absence of other causes of pre-capillary PH. Evidence presented in this briefing generally refers to PAH rather than to all types of PH, although the European Society of Cardiology (ESC) guidelines cover the whole range of PH.[1]

PAH is a serious and progressive disease characterised by increasing limitations on physical activity, right heart failure and premature death. Severity is often assessed based on WHO functional class, ranging from I to IV (Table 1). The assessment is subjective, based on the patient's answer to questions about limitations on their physical activity.

Class 1	Patients with PH but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnoea or fatigue, chest pain or near syncope.
Class 2	Patients with PH resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnoea or fatigue, chest pain or near syncope.
Class 3	Patients with PH resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnoea or fatigue, chest pain or near syncope.
Class 4	Patients with PH with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnoea and/or fatigue may be present even at rest. Discomfort is increased by any physical activity.

Table 1. Functional classification of PH[1]

In recent years a number of drugs have been licensed for the treatment of PAH in adults. The most important drug classes are prostanoids (beraprost, epoprostenol, iloprost and trepostinil), endothelin receptor antagonists (ambrisentan and bosentan) and phosphodiesterase type 5 (PDE5) inhibitors (sildenafil and tadalafil). All these drugs are expensive with costs ranging from around £5,000 to £120,000 annually. Another endothelin receptor antagonist, sitaxsentan, was withdrawn from the market in 2010 because of serious adverse effects and is not considered further in this briefing.

The current policy of the NHS in England is that treatment with these drugs is commissioned through specialist treatment centres for patients in functional classes III or IV. However, the ESC guidelines recommend treatment of patients in functional class II, giving their highest grade of recommendation (I-A) to ambrisentan, bosentan and sildenafil.[1] Furthermore, the Scottish Medicines Consortium (SMC) has recommended sildenafil[2] and ambrisentan[3] for the treatment of patients with functional class II PAH, although use of bosentan remains restricted.

It should be noted that the evidence grading system used by the ESC does not rate the quality and reliability of the supporting evidence. Class I is defined as 'evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective'. Level A evidence is defined as 'data derived from multiple randomized clinical trials or meta-analyses'.

The aim of this evidence briefing is to assess the evidence base for clinical and cost-effectiveness of targeted drug treatments for functional class II PAH. Treatment with combinations of drugs is excluded.

Methods

This briefing is a rapid appraisal and summary based mainly on existing sources of synthesised and quality-assessed evidence, primarily systematic reviews and economic evaluations. It is not a systematic review and we have not carried out exhaustive literature searches.

We searched for relevant research evidence in the following sources:

- DARE (Database of Abstracts of Reviews of Effects) for quality-assessed systematic reviews
- Cochrane Database of Systematic Reviews (CDSR)
- NHS EED for quality-assessed economic evaluations
- Health Technology Assessment (HTA) database

Although we did not systematically review the primary literature, data have been extracted from the report of the most relevant randomised trial to augment information from the most recent systematic reviews.

Evidence base for effectiveness

Systematic reviews

A broad search of CRD databases using terms for 'pulmonary hypertension' and 'pulmonary arterial hypertension' produced 76 records (35 systematic reviews in DARE, 21 economic evaluations in NHS EED and 20 records in the HTA database)

None of the systematic reviews dealt with functional class II PAH as their main focus. The identified reviews covered PAH as a condition and evaluated drug treatments in general,[4-6] specific drug classes[7, 8] or specific drugs.[9]

The most recent broad-based systematic review of drug therapy for PAH (latest search date November 2009) included 24 trials.[5] To be included, trials had to be double-blind randomised controlled trials (RCTs) with a follow-up of at least eight weeks. The comparator had to be placebo except for intravenous agents where the comparator could be usual therapy.

The included trials assessed prostanoids (11 trials, 1404 participants), endothelin receptor antagonists (eight trials, 1273 participants), PDE5 inhibitors (three trials, 950 participants) and other medications (one small trial each for terbogrel (71 participants) and rosuvastatin (60 participants)). The DARE critical appraisal indicated that this was a generally well-conducted review the findings of which are (as the authors acknowledge) limited by the small sample sizes and short follow-up of the included studies. The reported differences in six-minute walk distance and haemodynamic parameters are unlikely to be clinically meaningful. The review focused on mortality whereas this briefing focuses mainly on other outcomes for which more data are available for patients in functional class II.

Based on this systematic review, there is one published RCT that enrolled exclusively patients with functional class II PAH.[10] This trial (the EARLY study) compared bosentan with placebo for six months. Briefly, 93 patients were randomly assigned to bosentan and 92 to placebo. The primary outcomes were pulmonary vascular resistance and six-minute walk distance. At six months, geometric mean pulmonary vascular resistance was 83.2% (95% confidence interval 73.8 to 93.7) of the baseline value in the bosentan group and 107.5% (97.6 to 118.4) of baseline value in the placebo group. The reported net treatment effect of bosentan was -22.6% (-33.5 to -10.0). This was reported as statistically significant. Six-minute walk distance increased from baseline by 11.2 m (-4.6 to 27.0) in the bosentan group and decreased by 7.9 m (-24.3 to 8.5) in the placebo group. Baseline values were 438 m in the bosentan group and 431 m in the placebo group so the net treatment effect of 19.1 m (3.6 to 41.8) seems unlikely to be clinically significant. One patient in each group died during the trial. Sixty-five patients in the bosentan group had at least one adverse event compared with 60 in the placebo group; 20 patients reported serious adverse events, 12 in the bosentan group and eight in the placebo group.

Six other RCTs included in the review enrolled over 25% of patients in functional class II (Table 2). These included key trials of ambrisentan,[11] sildenafil[12] and tadalafil.[13] Additionally the small RCTs of terbogrel and rosuvastatin included 49% and 83% of patients in functional class II (not shown in Table 2).

Trial reference	Drug	Number of participants	Number in functional class II
Galiè 2002 (ALPHABET)[14]	Beraprost	130	64 (49.2%)
Barst 2003[15]	Beraprost	116	61 (52.6%)
Galiè 2008 (ARIES)[11]	Ambrisentan	393	151 (38.4%
Galiè 2008 (EARLY)[10]	Bosentan	185	185 (100%)
Galiè 2005 (SUPER)[12]	Sildenafil	278	108 (38.6%)
Simonneau 2008 (PACES)[16]	Sildenafil	267	71 (26.6%)
Galiè 2009 (PHIRST)[13]	Tadalafil	405	130 (32.1%)

Table 2. Representation of functional class II patients in RCTs of drugs for PAH (based on data extracted from Table 1 of the systematic review by Ryerson et al.[5])

Most RCTs in PAH have included a mixture of patients in different functional classes, mainly class II and III. It follows that the applicability of the results of these trials (except for the EARLY study) to patients in functional class II is uncertain and the same is true of systematic reviews based on these trials. Some data from a subgroup analysis of the main sildenafil trial were included in the manufacturer's submission to the SMC[2] but this included only 24 patients in functional class II at baseline.

Health technology assessments

Health technology assessments (HTAs) normally combine a systematic review of evidence on effectiveness with an economic evaluation or a review of economic evaluations. HTAs of drugs for PAH have been performed in various countries, including Poland,[17] Spain (Catalonia)[18] and Argentina.[19] We identified no HTA reports that dealt specifically with treatments for patients in functional class II.

The most relevant HTA report identified was published for the UK HTA Programme in 2009.[20] This covered epoprostenol, iloprost, bosentan, sitaxsentan and sildenafil within their licensed indications for the treatment of PAH. The authors found a 'paucity of data stratified by…functional class'. Hence one of the limitations identified in the report was uncertainty as to whether the effects of drug treatment differ significantly for patients in different functional classes. A further limitation is that new trials, notably the EARLY study, have been published since the report was prepared (last update February 2008).

The report identified only two RCTs that directly compared different drugs (bosentan vs. sitaxsentan and sildenafil vs. bosentan). No significant differences were found for any outcome in either trial. Data stratified by functional class were available only for the outcome of change in functional class in one trial.

In summary, there is a substantial amount of synthesised evidence for the clinical effectiveness of targeted drug treatments for PAH but most of the trials have involved mixed populations of patients in functional classes II and III. Hence there is uncertainty about the relevance of the findings for decisions on drug treatments for patients with functional class II PAH. The great majority of trials have compared targeted drug treatments with placebo or best supportive care alone rather than with each other.

Evidence base for cost-effectiveness

Economic evaluations

We found no published economic evaluations in NHS EED addressing cost-effectiveness of drugs in functional class II PAH. One generally well conducted economic evaluation concluded that bosentan was cost-effective, compared with no active intervention, for the treatment of functional class III PAH from the perspective of the UK NHS.[21] Two other published economic evaluations have not yet been critically appraised by NHS EED. Both appear to relate to the whole population of patients with PAH; furthermore one of the evaluations refers specifically to the Canadian health system[22] while the other

uses cost data from the US Medicare and Medicaid system,[23] so the relevance of the results to the UK NHS is uncertain. The Canadian study used a cost-minimisation analysis (assuming clinical equivalence) comparing sildenafil with bosentan, sitaxsentan and ambrosentan. The authors concluded that sildenafil was the cheapest agent but ambrisentan may have advantages over other endothelin receptor antagonists. The US study found that sildenafil was less costly and resulted in a greater gain in quality-adjusted life-years (QALYs) compared with other treatments.

SMC submissions

The SMC submissions for sildenafil[2] and ambrisentan[3] for class II PAH were supported by economic evidence submitted by the respective manufacturers. It appears that neither submission considered the option of no targeted drug treatment. Limited details of the analyses were reported, making it difficult to appraise the model. It may be worth approaching the SMC and/or the manufacturers for further details of the models included in both submissions.

Ambrisentan

For ambrisentan, the manufacturer submitted a discrete event simulation model to estimate a cost per QALY over a 5-year time horizon for ambrisentan compared with bosentan and sitaxsentan. The model related to patients with functional class II and III PAH. In this model, ambrisentan was dominant (i.e. it resulted in both lower costs and greater health benefits) compared with both bosentan and sitaxsentan. Ambrisentan was £20,987 cheaper than bosentan and produced 0.15 more QALYs. The model did not include sildenafil as a comparator.

The SMC expressed a number of concerns about this model but nevertheless accepted that ambrisentan is cost-effective compared with bosentan and sitaxsentan. The limited details reported make it difficult to comment in detail on the model.

Sildenafil

For sildenafil, the manufacturer submitted a cost-minimisation analysis comparing sildenafil with ambrisentan for patients with functional class II PAH treated in a designated Scottish Pulmonary Vascular Unit over a 1-year period. An indirect comparison used data on ambrisentan taken from a pooled analysis of relevant studies (no further details reported) and data on sildenafil from the SUPER trial.[12] The submission stated that there was no difference between the two treatments in the primary outcome measure of six-minute walking distance and therefore that these agents appear to be equally effective in this patient group. The ambrisentan data included patients in functional class III; the manufacturer assumed that ambrisentan would show the same benefits in the functional class II subgroup. Adverse events were assumed to be similar between the treatments and were not included in the analysis.

The submission gave NHS costs per patient per year as £6,056 for sildenafil (20 mg three times daily) and £21,840 for ambrisentan (5 mg), a cost saving of £15,784. This model assumed that 9% of patients treated with sildenafil would deteriorate and switch to an endothelin antagonist. In a sensitivity analysis that increased the probability of switching to an endothelin antagonist to 36%, the cost saving was reduced to £9,564.

The SMC queried the use of data from a mixed population of functional class II and III patients to estimate the benefits of ambrisentan in functional class II PAH. However, the data on clinical benefits were considered adequate and hence the economic case for sildenafil use was accepted.

Implications for the North of England Specialised Commissioning Group

General

Existing sources of synthesised evidence provide limited guidance on the clinical and cost-effectiveness of drug therapies for patients with functional class II PAH. A new systematic review focusing on patients in functional class II could be undertaken but this would require considerable resources and it is doubtful whether it would produce clearer evidence to guide decision-making. Given the uncertainties around the economic evidence, a new economic model (or if feasible a critical appraisal of the models supplied to the SMC) could also be helpful. As with further analysis of effectiveness data, the value of developing an economic model could be limited by the availability of evidence to populate the model.

Implementation

It is estimated that there are currently some 80 patients with functional class II PAH being treated at specialist centres in England. Commissioning treatment for these patients with the cheapest of the drugs approved by the SMC (sildenafil) would incur costs of (at least) approximately £500,000 per year. It is likely that there are patients outside the specialist treatment centres who would present for treatment if available but the number of patients involved is uncertain. There could also be a tendency to classify patients with relatively mild disease as class II rather than class I; again the potential impact on costs and outcomes is uncertain.

Other key uncertainties include whether targeted drug treatment would slow progression from functional class II to class III PAH and the rate of patients starting treatment with, for example, sildenafil moving on to treatment with a more expensive endothelin antagonist or a combination drug regimen. These issues and the uncertainties around them could potentially be investigated by economic modelling.

Health equity

The current policy of commissioning targeted drug treatments for patients in functional class III but not those in class II potentially raises equity issues because (1) assessment of functional class is subjective and patients could be treated differently depending on the centre/clinician who assesses them and (2) the approval of sildenafil and ambrisentan by the SMC means that patients with the same severity of PAH could be treated differently in England and Scotland. Equity considerations need to be balanced against the limitations of the current evidence and uncertainty as to whether further research in the form of evidence synthesis would provide a clear answer to guide decision-making.

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