Darbepoetin alfa (Aranesp) for anaemia in symptomatic heart failure – first line

February 2012

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The National Horizon Scanning Centre Research Programme is part of the National Institute for Health Research
Darbepoetin alfa (Aranesp) for anaemia in symptomatic heart failure – first line

Target group

Technology description
Darbepoetin alfa (Aranesp; darbepoetin-α; Nespo; NESP) is a modified analogue of the erythropoiesis-stimulating agent (ESA) epoetin, which contains two additional N-glycosylation sites allowing prolonged clearance and less frequent administration. A putative reduction in erythropoietin (EPO) production and increased resistance to the actions of EPO in anaemia associated with HF suggest that ESAs may be a pertinent treatment option. If licensed, darbepoetin alfa will be administered subcutaneously, to achieve and maintain a haemoglobin concentration (Hb) of at least 13g/dL, and not to exceed 14.5g/dL. It is administered every two weeks at a starting dose of 0.75µg/kg until Hb is within the target range, then the administration is extended to every month and the dose titrated to maintain Hb within the target range.

Darbepoetin alfa is licensed for the treatment of symptomatic anaemia in patients with chronic renal failure, and for symptomatic chemotherapy-induced anaemia in cancer patients. The most common adverse events (AEs) associated with darbepoetin alfa when used for these indications include hypersensitivity; stroke; hypertension; thromboembolic events, including pulmonary embolism; rash or erythema; oedema; and injection site pain.

Innovation and/or advantages
There are currently no recommended pharmacological treatment options for anaemia in patients with HF other than the treatment for iron deficiency. If licensed, darbepoetin alfa would offer a possible therapeutic approach.

Developer
Amgen Limited.

Availability, launch or marketing dates, and licensing plans
In a phase III clinical trial.

NHS or Government priority area
This topic is relevant to the National Service Framework for Coronary Heart Disease (2005) and the National Service Framework for Older People (2001).

Relevant guidance

Clinical need and burden of disease
HF is characterised by breathlessness, fatigue, and fluid retention. The quality of life experienced by people with HF is generally worse than that for people with other chronic conditions, such as arthritis or chronic lung disease. Many patients with HF suffer from anaemia due to renal failure, erythropoietin resistance, reduced erythropoietin secretion (including that due to angiotensin-converting enzyme inhibitor use) and extracellular fluid expansion. Increased myocardial workload due to haemodynamic and neuro-hormonal alterations observed in chronic anaemia can cause increased left ventricle (LV) mass, adverse LV remodelling and dysfunction which result in worsening congestive HF with an increased mortality risk. Anaemia, defined as a Hb concentration <12g/dL in women and <13g/dL in men, occurs in 25-60% of HF patients. The prevalence of anaemia increases with HF severity, advanced age, female sex, renal disease, and other co-morbidities. It is associated with poorer outcomes, decreased exercise capacity, and poor quality of life. Anaemia in HF increases the risk of hospitalisation or death by 30-60%.

It is estimated that there are 63,000 new cases of HF in the UK each year, of whom around 34,000 are in men and 29,000 are in women. During 2010-11 the number of patients with HF on primary care disease registers in England was 392,853, resulting in an unadjusted prevalence of 0.7%. In England in 2010-11, there were 60,000 hospital admissions for HF (ICD10 I50) resulting in 550,820 bed days and 739,668 finished consultant episodes. The prognosis for HF is poor, with 30-40% of those diagnosed dying within a year.

Existing comparators and treatments
Correction of anaemia has not been established as routine therapy in HF. Simple blood transfusion is not recommended to treat the anaemia of chronic disease in HF. Among potential therapies, the use of ESAs (usually together with iron) to increase red blood cell production represents an unproven option. A systematic review of nine trials totalling 3,167 patients found little evidence that the use of ESAs improved health outcomes in patients with heart disease. Specialist referral is recommended for the treatment of HF with left ventricular systolic dysfunction (LVSD) when anaemia is also a co-morbidity.

Efficacy and safety

<table>
<thead>
<tr>
<th>Trial</th>
<th>Sponsor</th>
<th>Status</th>
<th>Source of information</th>
<th>Location</th>
<th>Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>RED-HF, NCT00358215, 20050222; darbepoetin alfa or placebo; phase III.</td>
<td>Amgen Limited.</td>
<td>Ongoing.</td>
<td>Publication, trial registry, manufacturer.</td>
<td>EU (inc UK), USA, Canada and other countries.</td>
<td>Randomised, placebo-controlled.</td>
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<tr>
<td>STAMINA-HeFT, NCT00049985, 20010170; darbepoetin alfa or placebo; phase II.</td>
<td>Amgen Limited.</td>
<td>Published.</td>
<td>Publication, trial registry, manufacturer.</td>
<td>EU (inc UK), USA, Canada and Australia.</td>
<td>Randomised, placebo-controlled.</td>
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* Expert communication.
Participants and schedule  

Participants and schedule  
n=2,600 (planned); ≥18 years; anaemia; symptomatic HF; symptomatic LSVD. Randomised to darbepoetin alfa, starting dose 0.75µg/kg, every 2 weeks until Hb of 13.0g/dL achieved, and then monthly dose titration to maintain Hb (Hb not to exceed 14.5g/dL), or placebo, both given subcutaneously for the duration of the trial.

Follow-up  

Event-driven study with treatment duration expected to be a maximum of 81 months.

Primary outcome  

Composite outcome of time to death from any cause or first hospital admission for worsening HF.

Secondary outcomes  

Time to death from any cause; time to cardiovascular death or first hospital admission for worsening HF; change in Kansas City Cardiomyopathy Questionnaire (KCCQ) Overall Summary Score; change in KCCQ Symptom Frequency Score.

Key results  

For darbepoetin alfa (n=162) vs placebo (n=157) at week 27, respectively: mean change in exercise duration adjusted for baseline exercise duration, 57.3s (95% CI, 37.5-77.1) vs 46.5s (95% CI, 25.9-67.2), p=0.46; change in NYHA functional class (SE), -0.19 (0.04) vs -0.13 (0.04), p=0.34; proportion reporting improvement in PGA score, 71% vs 71%, p=0.95; change in MLHFQ total score (SE), -9.3 (1.6) vs -7.1 (1.9), p=0.38.

Adverse effects (AEs)  

Darbepoetin alfa vs placebo (%), respectively: serious AEs (47 vs 52); worsening HF (23 vs 29); hypertension (8 vs 6); myocardial infarction (2 vs 3); stroke (2 vs 2); transient ischemic attack (2 vs 1); subarachnoid haemorrhage (1 vs 0); intracranial haemorrhage (1 vs 0); seizure (1 vs 1); death (7 vs 11).

Expected reporting date  

March 2013.

Trial  

NCT00086086, 20020171; darbepoetin alfa or placebo; phase II.

Sponsor  

Amgen Limited.

Status  

Published.

Source of information  

Publication25, trial registry26, manufacturer.

Location  

EU (inc UK) and USA.

Design  

Randomised, placebo-controlled.

Trial  

NCT00117234, 20020126; darbepoetin alfa or placebo; phase II.

Sponsor  

Amgen Limited.

Status  

Published.

Source of information  

Publication27, trial registry28, manufacturer.

Location  

EU (inc UK).

Design  

Randomised, placebo-controlled.
<table>
<thead>
<tr>
<th>Participants and schedule</th>
<th>n=165; ≥21 years; anaemia; symptomatic HF; symptomatic LVSD. Randomised to a weight-based dose of darbepoetin alfa, starting dose 0.75µg/kg, titrated to achieve a Hb of 14.0±1.0g/dL; a fixed dose of darbepoetin alfa, starting dose 50µg, titrated to achieve a Hb of 14.0±1.0g/dL; or placebo, all given subcutaneously every 2 weeks for 25 weeks, supplemented with 200mg/day of elemental oral iron (unless baseline serum ferritin &gt;800µg/L).</th>
<th>n=41; ≥21 years; anaemia; symptomatic HF; symptomatic LVSD. Randomised to darbepoetin alfa, starting dose 0.75µg/kg, titrated to achieve a Hb of 14.0±1.0g/dL, or placebo, both given subcutaneously every 2 weeks for 26 weeks, supplemented with 200-300mg/day of elemental oral iron (unless baseline serum ferritin &gt;800ng/ml).</th>
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</thead>
<tbody>
<tr>
<td>Follow-up</td>
<td>Active treatment period 25 weeks, then 4 weeks follow-up.</td>
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<tr>
<td>Primary outcome</td>
<td>Rate of rise in Hb.</td>
<td>Exercise tolerance, measured as peak oxygen consumption (VO₂) at 26 weeks.</td>
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<td>Secondary outcomes</td>
<td>Change in left ventricular ejection fraction (LVEF); change in 6-minute walk distance; NYHA classification; PGA, MLHFQ and KCCQ scores.</td>
<td>Exercise duration; NYHA classification; PGA, MLHFQ and KCCQ scores, all at 27 weeks.</td>
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<td>Key results</td>
<td>For darbepoetin alfa weight-based dose (n=56) and darbepoetin alfa fixed dose (n=54), combined vs placebo (n=55), respectively: improvement in KCCQ total symptom score, 8.2 vs 1.5 points, (p=0.027); non-significant improvements in 6-minute walk distance and PGA score; no improvement in NYHA class, LVEF and MLHFQ scores.</td>
<td>For darbepoetin alfa (n=19) vs placebo (n=22), respectively: mean change in Hb at week 27 (±SE), 2.4±0.4g/dL vs 0.9±0.5 g/dL (p=0.005); no change in peak VO₂ and exercise tolerance; improvement in self-reported PGA, 79% vs 41% (p=0.01); no improvement in KCCQ and MLHFQ scores.</td>
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<td>Adverse effects (AEs)</td>
<td>Darbepoetin alfa weight-based dose vs darbepoetin alfa, fixed dose vs placebo (%), respectively: congestive HF (16 vs 6 vs 16); hypertension (4 vs 0 vs 4); myocardial infarction (2 vs 2 vs 0); death (9 vs 2 vs 0).</td>
<td>Darbepoetin alfa vs placebo (%), respectively: serious AEs (21 vs 23); neurological signs (21 vs 5); upper respiratory tract infections (16 vs 0); cough (11 vs 18); joint-related symptoms (11 vs 0); other musculoskeletal and connective tissue symptoms (11 vs 18); hypertension (5 vs 0); congestive HF (5 vs 9); cerebrovascular disorder (5 vs 0); death (5 vs 5).</td>
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A pooled analysis of two phase II studies NCT00049985 (STAMINA-HeFT) and NCT00086086, suggested that darbepoetin alfa was associated with a reduction in the composite endpoint of all-cause mortality and hospitalisation for HF worsening, but this result was not statistically significant²⁹.

**Estimated cost and cost impact**

The cost of darbepoetin alfa for this indication is not yet known. However, darbepoetin alfa for the treatment of symptomatic anaemia in chronic renal failure and chemotherapy-induced anaemia in cancer patients would cost £88.90 for a single dose at 0.75µg/kg,³⁰.

³⁰ Based on average surface area 1.7m².
Claimed or potential impact – speculative

Patients

- Reduced mortality or increased length of survival
- Reduction in associated morbidity or improved quality of life for patients and/or carers
- Quicker, earlier or more accurate diagnosis or identification of disease

Other:

- None identified

Services

- Increased use
- Service organisation: Injection required.
- Staff requirements

Decreased use

- Other:
- None identified

Costs

- Increased unit cost compared to alternative
- Increased costs: more patients coming for treatment
- Increased costs: capital investment needed

- New costs:
- Savings:
- Other:

Other issues

- Clinical uncertainty or other research question identified:
- None identified

References


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