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Mepolizumab (Bosatria) for hypereosinophilic syndrome – first line in combination with corticosteroids

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Mepolizumab (Bosatria) for hypereosinophilic syndrome – first line in combination with corticosteroids

Target group

- Hypereosinophilic syndrome (HES): - first line; in combination with corticosteroids as a steroid sparing treatment in patients without the FIP1 gene.

Background

Hypereosinophilic syndrome (HES) is a collection of rare and heterogeneous disorders characterised by[1]:

- a persistent eosinophil (a type of white blood cell) count of >1500 cells/μl for more than 6 consecutive months (normal range: 350 cells/μl)
- eosinophil-mediated end-organ damage - accumulation of eosinophils causes inflammatory damage to infiltrated organs most frequently the heart, lung, skin, and nervous and gastrointestinal systems.
- exclusion of known secondary causes of hypereosinophilia such as infection, asthma, allergic reaction, haematological malignancies or Churg-Strauss Syndrome.

Subtypes of HES are recognised: the myeloproliferative form associated with the Fip1-like 1-platelet-derived growth factor receptor [FIP1L1-PDGFRA], a fusion gene which affects myeloid cells, and the lymphocytic form involving lymphoid cells[2]. Therapeutic strategies are based on this distinction. Symptoms can be non-specific such as fatigue, cough, rash and fever; but can include life-threatening cardiac symptoms. If left untreated HES can be rapidly fatal, but it can also take a slower course in some patients.

Idiopathic tissue or organ-specific eosinophil-mediated disorders e.g. eosinophilic oesophagitis are sometimes isolated from the definition of HES given their tendency to recur only in the initially affected organ.

Technology description

Mepolizumab (Bosatria) is a humanised anti-interleukin (IL)-5 monoclonal antibody. IL-5 stimulates the production, activation and maturation of eosinophils. Mepolizumab binds and inactivates free IL-5 leading to a sustained reduction in the numbers of circulating eosinophils. Mepolizumab is administered intravenously (IV) at a dose of 750mg at minimum of every 4 weeks.

Mepolizumab is also in phase II trials for asthma (in patients with airway eosinophilia) and eczema, but despite demonstrating reductions in eosinophils, this has so far not translated into clinical improvement[3,4]. Further studies in severe airways conditions associated with pulmonary eosinophilia are underway.

Innovation and/or advantages

Corticosteroids are widely used in the long-term treatment of the lymphocytic form of HES, but are associated with serious side effects. Mepolizumab is intended to minimise these adverse effects by reducing the dose of corticosteroids required.

Developer

GlaxoSmithKline.

Availability, launch or marketing dates, and licensing plans:

Orphan drug status for first line treatment in HES was granted in the EU in July 2004. Currently in phase III clinical trials.

Relevant guidance

No relevant guidance on HES was identified.

Clinical need and burden of disease

HES is a rare disorder. No data has been identified on the incidence or prevalence of HES in the UK, but it is estimated that there may be between 200-500 patients in England and Wales[a]. Over a period of 11 years the US National Institute of Health identified only 50 cases, but another US study found a prevalence of around 2,000 cases on the basis that approximately one-third of patients with eosinophilia had comorbid diagnoses compatible with HES[5]. HES is more common in men than women (ratio 9:1) and although the age of onset is variable, diagnosis usually occurs between the ages of 20 and 50[6]. Ten year survival rates are reported at around 42%[7]. Approximately 86% of patients with HES are negative for the FIP1L1-PDGFRA gene[8], and therefore may be eligible for treatment with mepolizumab.

Existing comparators and treatments

Except for the myeloproliferative variant of HES (for which imatinib mesylate is licensed as a first-line therapy), systemic oral corticosteroids (unlicensed) are frequently used in both the initial and long-term management of HES. Prolonged use of steroids is limited by potentially serious side effects including osteoporosis, infections and adrenal insufficiency, especially when used in high doses. In unresponsive cases, interferon alpha or other chemotherapeutic agents are sometimes used.

Efficacy and safety

Trial	Mepolizumab vs placebo Study 185/NCT00086658[9]. Phase III. Long-term extension safety and efficacy study 901/NCT00097370[10] (excludes: Churg Strauss Syndrome (CSS)).	Compassionate use in refractory severe HES[11]. NCT 00244686. Phase III (excludes: CSS; eosinophilic gastroenteritis; atopic disorders	Mepolizumab in adults with HES[12]; NCT 00266565. Phase II (includes: CSS; eosinophilic gastroenteritis; EO)
Sponsor	GlaxoSmithKline	GlaxoSmithKline	Children's Hospital Medical Centre (Cincinnati)
Status	Published (extension study 901 ongoing)	Ongoing	Ongoing
Location	USA, Europe, Canada, Australia	USA	USA
Design	Randomised, double blind placebo-controlled. Extension study (901) – uncontrolled; open-label	Non-randomised, uncontrolled, open-label.	Non-randomised, uncontrolled, open-label.
Participants in trial	n=85; eosinophilia-related organ involvement; negative for FIP1L1-PDGFRA gene. Run in period 6 weeks -	n=50; 12 years and older; demonstrated prior benefit with IL-5 but unsuitable for	n=24; mepolizumab 10mg/kg once a month for 3 months.

[a] Company estimate

	existing non-steroidal medications discontinued; corticosteroid monotherapy initiated (20-60mg/day) until stable clinical status. Randomised to 750mg IV mepolizumab or placebo every 4 weeks for 36 weeks (final infusion week 32). Prednisolone dose tapered until week 32.	continuation study 901.	
Follow-up	3 months after final dose. Study 901 - continues over 1-3 years.	-	8 years
Primary outcome	Study 185: Stable disease with reduction in prednisolone dose to ≤10mg/day for ≥8 consecutive weeks. Study 901: Frequency of all adverse effects	Incidence and severity of adverse effects	IL-5 toxicity
Secondary outcomes	Study 185: Blood eosinophil level <600/μl for 8 or more consecutive weeks; time to treatment failure; prednisolone dose ≤7.5mg/day. Study 901: Durable effect on prednisolone dose level; durable reduction in eosinophil count; optimal dosing frequency.	Change in end organ assessments; eosinophil count control; disease control; HES medications.	Reduction in peripheral blood eosinophils; steroid or interferon alpha sparing effect
Key results	Study 185: Primary endpoint met: 84% mepolizumab vs 43% placebo (95% CI: 1.59 to 5.26; p<0.001); eosinophil level reduced in 95% mepolizumab vs 45% placebo (p<0.001). Steroids stopped 47% mepolizumab vs 5% placebo (p<0.001). Majority remaining secondary endpoints met.	-	-
Expected reporting date	Study 901: December 2009	July 2009	April 2010
Adverse effects	Serious AE - 7 patients receiving mepolizumab (14 events, including 1 death – cardiac arrest not considered to be treatment related) and 5 patients (7 events) receiving placebo. Commonly reported AE in both groups included fatigue, pruritis, headache, arthralgia.	-	-

Estimated cost and cost impact

The cost of mepolizumab is currently unknown. The cost will be in addition to steroids, and IV administration will incur additional costs but can be performed on an outpatient basis. Potential for savings if steroid dose can be reduced, which could bring a reduction in the cost of steroid-associated adverse effects.

The annual cost of prednisolone ranges from £30-£200 per patient[b], based on a dose of 20-60mg per day.

Potential or intended impact – speculative

Patients

☑ Reduced morbidity	☐ Reduced mortality or increased survival	☑ 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 reorganisation required	☑ Staff or training required
☐ 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: Potential reduction in steroids – associated adverse effects.	☐ Other:

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[b] British National Formulary No. 55, March 2008

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The National Horizon Scanning Centre,
Department of Public Health and Epidemiology
University of Birmingham, Edgbaston, Birmingham, B15 2TT, England
Tel: +44 (0)121 414 7831 Fax +44 (0)121 414 2269
www.pcpoh.bham.ac.uk/publichealth/horizon