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HEALTH TECHNOLOGY BRIEFING JANUARY 2020

Mepolizumab for hypereosinophilic syndrome – add-on therapy

NIHRIO ID	20556	**NICE ID**	9918
Developer/Company	GlaxoSmithKline UK Ltd	**UKPS ID**	648705

Licensing and market availability plans	Currently in phase III clinical trials.

SUMMARY

Mepolizumab is a medicinal product currently in development as an add-on for the treatment of hypereosinophilic syndrome (HES). HES is a rare group of inflammatory disorders characterised by an overproduction of eosinophils (a type of disease-fighting white blood cell). When eosinophils infiltrate certain tissues, they can cause inflammation and organ damage which, over time, can impact patients' day-to-day ability to function. Although any organ system can be involved in HES, the heart, central nervous system, skin, and respiratory tract are the most commonly affected.

Mepolizumab is given by injection and works by blocking the activity of human interleukin-5 (IL-5), an immune protein that is responsible for the production and survival of eosinophils. By blocking the activity of IL-5, the production and survival of the eosinophils is reduced. Using mepolizumab in addition to the standard of care may improve outcomes and reduce symptoms in patients with HES.

PROPOSED INDICATION

For the treatment of hypereosinophilic syndrome, as an add-on therapy to standard of care.[a]

TECHNOLOGY

DESCRIPTION

Mepolizumab (Nucala) is a humanised monoclonal antibody (IgG1, kappa), which targets human interleukin-5 (IL-5) with high affinity and specificity. IL-5 is the major cytokine (immune protein) responsible for the growth and differentiation, recruitment, activation and survival of eosinophils (disease-fighting white blood cell). Mepolizumab inhibits the bioactivity of IL-5 with nanomolar potency by blocking the binding of IL-5 to the alpha chain of the IL-5 receptor complex expressed on the eosinophil cell surface, thereby inhibiting IL-5 signalling and reducing the production and survival of eosinophils.[1]

Mepolizumab is currently in development for the treatment of patients with hypereosinophilic syndrome (HES). In the phase III randomised trial (NCT02836496), patients received either 300mg of mepolizumab (powder reconstituted in sterile water) via subcutaneous (SC) injection or a placebo matching mepolizumab via SC injection in addition to standard of care (SOC) every 4 weeks for 32 weeks.[2]

INNOVATION AND/OR ADVANTAGES

Currently available therapies for HES, including glucocorticoids (GC), and immunomodulatory and cytotoxic therapies, have variable efficacy and significant toxicity. Safe and effective therapies that target eosinophils are clearly required. Mepolizumab is a monoclonal antibody to IL-5 developed for the treatment of asthma. Although early asthma trials failed to meet clinical efficacy endpoints, the reduction in absolute eosinophil count (AEC) and tissue eosinophilia was observed, prompting several small studies of anti-IL-5 therapy in HES.[3]

The phase III study (NCT02836496) met its primary endpoint, demonstrating a statistically significant result with 50% fewer patients experiencing a HES flare (worsening of symptoms or eosinophil threshold requiring an escalation in therapy) when treated with mepolizumab, compared to placebo, when added to SOC treatment over the 32-week study period (56% vs 28%; p=0.002).[4]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

In the UK, mepolizumab is currently licensed as an add-on treatment for severe refractory eosinophilic asthma in adults, adolescents and children aged 6 years and older.[1]

Headache is the most common (≥10%) adverse event associated with mepolizumab treatment. Other common (≥1%) adverse events associated with mepolizumab treatment include: lower respiratory tract infection, urinary tract infection, pharyngitis, hypersensitivity reactions, nasal congestion, upper abdominal pain, eczema, back pain, administration-related reactions, local injection site reactions and pyrexia.[1]

Mepolizumab is in phase II and phase III development as add-on treatment for several indications including:[5]

- Chronic Obstructive Pulmonary Disease (COPD)

[a] Information provided by GlaxoSmithKline UK Ltd

- Eosinophilic Esophagitis
- Eosinophilic Bronchitis
- Eosinophilic granulomatosis with polyangitis (EGPA) Syndrome
- Nasal Polyps
- Bullous Pemphigoid

Mepolizumab was designated an orphan drug status in the EU for HES in 2004.[6]

PATIENT GROUP

DISEASE BACKGROUND

HES is a rare group of inflammatory disorders that affects approximately 20,000 people globally. Patients with the condition have a persistent and marked overproduction of eosinophils, (> 1.5 × 10^9/L for more than six consecutive months) associated with evidence of eosinophil-induced organ damage, where other causes of hypereosinophilia such as allergic, parasitic, and malignant disorders have been excluded.[4,7] When eosinophils infiltrate certain tissues, they can cause inflammation and organ damage which, over time, can impact patients' day-to-day ability to function.[4] Although any organ system can be involved in HES, the heart, central nervous system, skin, and respiratory tract are the most commonly affected.[8]

The signs and symptoms of HES can vary significantly depending on which part(s) of the body are affected. Frequent symptoms listed by body system include:[8]

- Skin - rashes, itching, and oedema.
- Lung - asthma, cough, difficulty breathing, recurrent upper respiratory infections, and pleural effusion.
- Gastrointestinal - abdominal pain, vomiting, and diarrhoea.
- Musculoskeletal - arthritis, muscle inflammation, muscle aches, and joint pain.
- Nervous system - vertigo, paraesthesia, speech impairment, and visual disturbances.
- Heart - congestive heart failure, cardiomyopathy, pericardial effusion, and myocarditis.
- Blood - deep venous thrombosis, and anaemia.

Affected people can also experience a variety of non-specific symptoms such as fever, weight loss, night sweats and fatigue.[8]

In approximately 3/4 of cases, the underlying cause of HES still remains unknown. However, recent advances in diagnostic techniques have led researchers to believe that some people affected by HES may have eosinophilia due to a variety of causes, including:[8]

- Myeloproliferative neoplasms or other disorders that affect the bone marrow (myeloproliferative disorders). This form is called myeloproliferative HES. The majority of these patients have been found to have a gene fusion of the gene Fip1-like 1 (FIP1L1) and the gene platelet-derived growth factor receptor alpha (PDGFRα) AKA F/P. This F/P fusion gene causes expansion of the eosinophil population, leading to HES. This F/P type pf HES disproportionately affects males.[9]
- Increased production of interleukin-5 (IL-5) (a protein produced by certain types of white blood cell). This form is called lymphocytic HES.
- A change (mutation) in an unknown gene passed down through a family. This form is called familial HES.

Patients with F/P-associated disease often present with heart involvement and mucosal ulcers, and are overall more likely to develop disease-related morbidity and mortality, whereas patients with lymphocytic HES often present predominantly with cutaneous (skin) manifestations, while their cardiovascular system is often spared. As for long-term

haematological outcome, patients with F/P-associated disease are at risk for developing acute leukaemia (eosinophilic or myeloid), at times shortly after diagnosis of HES, while patients with lymphocytic HES are at risk of developing T-cell lymphoma, generally after many years of indolent (idle) pre-malignant disease. Currently, prognosis depends on two major aspects of disease: heart involvement and the increased likelihood of developing haematological malignancies.[7]

CLINICAL NEED AND BURDEN OF DISEASE

HES is a rare and under-diagnosed disorder, making it difficult to estimate prevalence.[7] However, data analysis in 2019 estimated the EU incidence rate for HES to be 1.5 in every 100,000 people.[10] The population of the UK in 2018 was estimated at 66,435,600 people.[11] Applying the HES data to the population of the UK in 2018 estimate, approximates that the number of people in the UK with HES to be about 996 people.

In the paediatric population, HES predominantly affects males. However, in the adult population, HES appears to affect males and almost equally, with an estimated male to female ratio of around 1.2 to 1.[12,13] Disease tends to occur in patients aged from 20 to 50, but all age groups may be concerned.[7]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

The treatment and management of HES varies based on the severity of the condition and if an underlying cause for the eosinophilia has been identified.[8]

Affected people without the FIP1L1/PDGFRA fusion gene are typically treated with corticosteroids initially. Approximately one third of these cases do not respond to steroids so other agents, such as hydroxyurea, interferon-alpha, and imatinib, may be administered.[8]

In people who are affected by HES that do not respond to standard treatments, other therapies may be tried, including chemotherapy and hematopoietic stem cell transplantation; however, there is little data regarding the effectiveness of these treatments so they are not routinely given.[8]

Treatment of idiopathic HES (HES of unknown cause) consists of first line corticosteroids. Immunomodulatory and myelosuppressive agents are reserved for steroid-unresponsive disease or are used as adjuvant steroid-sparing therapy.[14]

The treatment of lymphocytic variant HES consists of corticosteroids first line. Ciclosporin (an immunosuppressant) may be useful as a steroid-sparing agent.[14]

CURRENT TREATMENT OPTIONS

Prednisolone is a corticosteroid indicated for the treatment and/or suppression of inflammatory and allergic disorders.[15] It is utilised as a treatment in HES.[2,14]

Imatinib is a tyrosine kinase inhibitor indicated for the treatment of adult patients with advanced HES and/or chronic eosinophilic leukaemia with FIP1L1-PDGFRα (P/F) rearrangement.[16]

PLACE OF TECHNOLOGY

If licensed, mepolizumab will offer an additional treatment option for patients with HES, who currently have few well-tolerated and effective therapies available.

CLINICAL TRIAL INFORMATION

Trial	NCT02836496; 2014-001232-11; **adolescents and adults aged ≥ 12 years; mepolizumab vs placebo, on top of SOC; phase III.**
Sponsor	GlaxoSmithKline
Status	Completed
Source of Information	Trial registry,[2] manufacturer[4]
Location	EU (incl. UK), USA and other countries.
Design	Randomised, double-blind, placebo-controlled, parallel group,
Participants	N=108; aged 12 years and older; male or female; severe HES; diagnosed for ≥6 months; ≥2 HES flares in the past 12 months; blood eosinophil count of ≥1000 cells/μL.
Schedule	Patients randomised to mepolizumab 300mg lyophilized powder reconstituted with water for SC injection every 4 weeks of 32 week treatment period; or 0.9% sodium chloride solution placebo SC injection; both on top of SOC (5mg prednisolone or prednisone).
Follow-up	Active treatment every 4 weeks for 32 weeks, follow-up 8 weeks.
Primary Outcomes	Proportion of subjects who experience an HES flare during the 32-week study treatment period [Time Frame: Up to 33 weeks].
Secondary Outcomes	• Time to first HES flare [Time Frame: Up to 33 Weeks] • Proportion of subjects who experience an HES flare during Week 20 through Week 32 [Time Frame: From Week 20 until Week 32] • Number of HES flares per subject per year [Time Frame: Baseline (randomization) and up to 33 Weeks] • Change from baseline in fatigue severity based on Brief Fatigue Inventory (BFI) item 3 (worst level of fatigue during past 24 hours) at Week 32 [Time Frame: Baseline and up to Week 32]
Key Results	Primary end point met: 50% fewer patients experiencing a HES flare (worsening of symptoms or eosinophil threshold requiring an escalation in therapy) when treated with mepolizumab, compared to placebo, when added to standard of care treatment over the 32-week study period (56% vs 28%; p=0.002). Secondary endpoints from the study were also statistically significant and supported the primary endpoint, showing: • Risk of first HES flare over the study period was 66% lower for patients treated with mepolizumab compared to placebo (hazard ratio 0.34; 95% CI 0.18, 0.67). • There was a 66% reduction in the annualised rate of HES flares versus placebo (rate ratio 0.34; 95% CI 0.19, 0.63).

	• Fatigue scores improved in mepolizumab compared to placebo (p=0.036). • The safety results in the study were consistent with the known profile of mepolizumab.
Adverse effects (AEs)	Not reported
Expected reporting date	-

ESTIMATED COST

Mepolizumab is already marketed in the UK for severe refractory eosinophilic asthma. The NHS list price for mepolizumab is:[17]
Solution for injection:

- 100mg/1ml solution for injection pre-filled pen - £840.00
- 100mg/1ml solution for injection pre-filled syringes - £840.00

Powder for solution for injection:

- 100mg powder for solution for injection vials - £840.00 (Hospital only)

Note: The expected licensed dose for HES will be 300mg every 4 weeks in line with the clinical trial dosage.[b]

RELEVANT GUIDANCE

NICE GUIDANCE

No NICE guideline has been identified

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

No guidelines/policy identified.

OTHER GUIDANCE

- British Journal of Haematology. Guideline for the investigation and management of eosinophilia. 2017.[14]

ADDITIONAL INFORMATION

[b] Information provided by GlaxoSmithKline UK Ltd

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