Mepolizumab (Nucala) for relapsed or refractory eosinophilic granulomatosis with polyangiitis – second line add on therapy

LAY SUMMARY

Eosinophilic granulomatosis with polyangiitis is a rare disease that causes inflammation of small and medium sized blood vessels. The lungs and skin are commonly affected, but it can affect other organs including the heart, kidneys, nerves and bowels. Symptoms can include high temperature, tiredness, muscle and joint pain, shortness of breath, rapid weight loss, and skin rash.

Mepolizumab is a new drug for the treatment of eosinophilic granulomatosis with polyangiitis that is given as an injection under the skin. Some studies have suggested mepolizumab may be helpful for people whose first treatment has failed.

NIHR HSRIC ID: 9670
TARGET GROUP

- Eosinophilic granulomatosis with polyangiitis (EGPA): relapsed or refractory – second line; add on therapy.

TECHNOLOGY

DESCRIPTION

Mepolizumab (Nucala; SB-240563) is an anti-interleukin-5 fully humanised IgG1 monoclonal antibody. Interleukin-5 stimulates the production, activation and maturation of eosinophils. Mepolizumab binds to interleukin-5 with high specificity to inhibit its signalling. This causes a sustained reduction in the numbers of circulating eosinophils and is therefore intended to be used in conditions characterised by increased levels of eosinophils. Mepolizumab is administered by subcutaneous (SC) injection at 100mg every 4 weeks\(^a\).

Mepolizumab (as Nucala) is licensed in the EU as an add-on treatment for severe refractory eosinophilic asthma in adult patients. Very common and common (≥1%) reported adverse events include headache, lower respiratory tract infection, urinary tract infection, pharyngitis, nasal congestion, abdominal pain, eczema, back pain, local injection site reactions, and pyrexia\(^1\).

Mepolizumab is also currently in phase III development for the treatment of chronic obstructive pulmonary disease with eosinophilic bronchitis, and phase II development for asthma in children and nasal polyps.

INNOVATION and/or ADVANTAGES

Expert opinion suggests that while current induction strategies for EGPA are well-defined and remission rates are good, relapses remain common and there is a need to optimise long-term maintenance therapy and prevent chronic damage\(^b\). If licensed, mepolizumab will offer an additional subcutaneous treatment option for patients with relapsed or refractory EGPA.

DEVELOPER

GlaxoSmithKline UK.

AVAILABILITY, LAUNCH OR MARKETING

Mepolizumab is a designated orphan drug in the EU and USA.

In phase III clinical trials.

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\(^a\) Company provided information.

\(^b\) Expert personal communication.
The primary systemic vasculitides are heterogeneous, multisystem disorders characterised by inflammation and necrosis of blood vessels. Their aetiology is unknown. Three distinct clinico-pathological syndromes, often associated with positive antineutrophil cytoplasmic antibody tests (ANCA-associated vasculitis), have been identified and collectively comprise the most common subgroups to affect small and medium-sized arteries: EGPA, granulomatosis with polyangiitis (GPA), and microscopic polyangiitis (MPA). EGPA is the rarest form of ANCA-associated vasculitis. Also known as Churg-Strauss syndrome, it is a systemic small vessel vasculitis associated with asthma and eosinophilic infiltration of the organ systems involved. Expert opinion states that hallmark features include a prodromal phase of asthma and/or ear, nose and throat disease, followed by serum and or tissue eosinophilia, and in some a vasculitic phase with vessel damage. Specific features depend on the target organ affected.

In 1990, the American College of Rheumatology defined classification criteria to distinguish the different vasculitides and identified six criteria for EGPA: asthma, eosinophilia of more than 10% in peripheral blood, paranasal sinusitis, pulmonary infiltrates, histological confirmation of vasculitis with extravascular eosinophils, and mononeuritis multiplex or polyneuropathy. When four or more of these criteria are met, vasculitis can be classified as EGPA. Other possible symptoms include fever, fatigue, muscle and joint pain, shortness of breath, rapid weight loss, and skin rash. Expert opinion states that EGPA can occur in children and adults, and has a mean onset between 30-50 years of age.

Expert opinion states that the burden of the disease depends on disease-related organ damage, in particular heart, lung, renal and peripheral neurological involvement that can lead to significant morbidity and in some mortality.

EGPA is a rare disease. In the UK, it has an annual incidence of 0.1 to 0.2 per 100,000 population, which equates to approximately 65 to 129 new diagnoses each year. Expert opinion notes that the overall prevalence of EGPA is lower than other ANCA associated vasculitis, and it has an estimated prevalence of 11-24 per million in Europe. If appropriately treated, the outcome of EGPA is good with respect to mortality; five- and 10-year survival rates are reported to be around 97% and 89%, respectively. However, disease-related organ damage (e.g. heart failure, chronic neuropathy) may severely impair the quality of life of patients.

In 2014-15, there were 487 hospital admissions due to EGPA (ICD-10 M30.1) in England, accounting for 586 finished consultant episodes and 1,228 bed days. In 2014, there were 35 deaths from CLL registered in England and Wales.

Expert personal communication.
PATIENT PATHWAY

RELEVANT GUIDANCE

NICE Guidance


NHS England Policies and Guidance


Other Guidance


CURRENT TREATMENT OPTIONS

Standard treatment for EGPA consists of inducing remission with high dose glucocorticoids and high dose oral or intravenous (IV) cyclophosphamide for three to six months, and maintaining remission with azathioprine, methotrexate or mycophenolate for approximately three to five years depending on clinical progress, while glucocorticoids are slowly reduced and withdrawn^d,^10. Approximately 75% of patients treated with daily oral cyclophosphamide and prednisolone achieve remission by three months; however, 50% of treated patients experience one or more relapses by five years^10. Rituximab can be used as a substitute for cyclophosphamide in the induction of remission^3.

Expert opinion states that a major practical issue with the treatment of patients with EGPA is that their care requires input from many specialities and many patients have difficulty accessing appropriate advice^d. Expert opinion also states that there is a current clinical need for alternative treatment pathways due to a high number of patients (>80%) requiring long-term treatment with steroids to reduce relapse risk^d. Long-term steroids can lead to multi-morbidity, including weight gain, cutaneous complications, hypertension, diabetes and poor bone health (osteoporosis and fractures)^d.

EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT02020889, 115921; mepolizumab vs placebo; phase III.</th>
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<tbody>
<tr>
<td>Sponsor</td>
<td>GlaxoSmithKline.</td>
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<tr>
<td>Status</td>
<td>Ongoing.</td>
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<tr>
<td>Source of information</td>
<td>Trial registry^11.</td>
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^d Expert personal communication.
Horizon Scanning Research & Intelligence Centre

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<tr>
<th>Location</th>
<th>EU (incl UK), USA, Canada and other countries.</th>
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<tr>
<td>Design</td>
<td>Randomised, placebo-controlled.</td>
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<tr>
<td>Participants</td>
<td>n=130 (planned); aged 18 yrs and older; EGPA; asthma with eosinophilia with ≥2 of the following additional features: biopsy showing histopathological evidence of EGPA, perivascular eosinophilic infiltration, eosinophil-rich granulomatous inflammation, neuropathy, pulmonary infiltrates, sinonasal abnormality, cardiomyopathy, alveolar haemorrhage, palpable purpura, or ANCA positivity; relapsed or refractory disease; no granulomatosis with polyangiitis (Wegener's granulomatosis) or microscopic polyangiitis; no organ or life-threatening EGPA; no current or previous history of cancer; no unstable liver disease, cirrhosis or known biliary abnormalities; no uncontrolled cardiovascular disease; no chronic or ongoing active infectious disease requiring systemic treatment; no known allergy or intolerance to a monoclonal antibody or biologic therapy.</td>
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<tr>
<td>Schedule</td>
<td>Randomised to mepolizumab 300mg SC every 4 wks; or placebo SC every 4 wks; both in combination with standard care.</td>
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<td>Follow-up</td>
<td>Active treatment for 1 yr.</td>
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<td>Primary outcomes</td>
<td>Duration of remission; proportion of subjects in remission at wks 36 and 48 of treatment period.</td>
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<td>Secondary outcomes</td>
<td>Time to first relapse; average daily prednisolone dose; proportion of subjects who achieve remission.</td>
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<td>Expected reporting date</td>
<td>Study completion date reported as Sept 2016.</td>
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**ESTIMATED COST and IMPACT**

**COST**

The cost of mepolizumab is not yet known.

**IMPACT - SPECULATIVE**

**Impact on Patients and Carers**

- Reduced mortality/increased length of survival
- Reduced symptoms or disability: expert opinion states that although EGPA is rare, it confers significant risk of morbidity and mortality. Therefore, effective treatment strategies are required in refractory/relapsing disease when conventional therapy fails. Furthermore, tailored EGPA regimes with mepolizumab (or rituximab) may facilitate treatment pathways which limit the use of steroids, which itself are associated with morbidity *

- Other
- No impact identified

* Expert personal communication.
Impact on Health and Social Care Services

- Increased use of existing services: expert opinion states that infrastructure is required to support administration of mepolizumab in secondary care or secondary care directed homecare service.
- Decreased use of existing services
- Re-organisation of existing services
- Need for new services
- Other
- None identified

Impact on Costs and Other Resource Use

- Increased drug treatment costs
- Reduced drug treatment costs
- Other increase in costs
- Other reduction in costs
- Other: uncertain unit cost compared to existing treatments.
- None identified

Other Issues

- Clinical uncertainty or other research question identified: expert opinion notes there are a number of potential areas to address including:
  - Would mepolizumab be more effective in specific subgroups of patients or those with adverse reactions to conventional treatment and/or steroid-dependent?
  - Is there a role for mepolizumab in paediatric EGPA? Potentially, response rates in juvenile-onset disease may be higher with mepolizumab and reduce long-term steroid exposure.
  - How will mepolizumab therapy be delivered? Homecare or hospital administration?
  - What is the optimal duration of mepolizumab treatment in relapsing refractory EGPA, after conventional treatment failure?
- None identified

REFERENCES

5 Vagilo A, Buzio C and Zwerina J. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss): state of the art. European Journal of Allergy and Clinical Immunology 2013;68(3)261-273.

* Expert personal communication.


