AWTTC
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

Mepolizumab (Nucala®) for the treatment of chronic eosinophilic pneumonia (OW15)

March 2021

ONE WALES INTERIM COMMISSIONING DECISION

Mepolizumab (Nucala®) for the treatment of chronic eosinophilic pneumonia

Date of advice: March 2021

The following Interim Pathways Commissioning Group (IPCG) recommendation has been endorsed by health board Chief Executives.

It is the view of the Interim Pathways Commissioning Group (IPCG) that mepolizumab (Nucala®) should continue to not be supported within NHS Wales for the treatment of chronic eosinophilic pneumonia.

Individual Patient Funding Request (IPFR) consideration remains appropriate for those patients who are likely to obtain significantly more clinical benefit from the intervention than would normally be expected at a reasonable value for money.

This advice will be reviewed after 12 months or earlier if new evidence becomes available.

One Wales advice promotes consistency of access across NHS Wales.

This is a summary of new evidence available and patient outcome data collected, to inform the review.

Background

Chronic eosinophilic pneumonia (CEP) is a rare disease that is part of a larger group of lung diseases characterised by abnormal infiltrations of eosinophils in the lungs. It is characterised by the progressive onset of symptoms including cough, dyspnoea, malaise, chest pain, fever and weight loss, over a few weeks[1]. It is usually successfully treated with corticosteroids but the disease can relapse on tapering or discontinuation of corticosteroids[2]. Mepolizumab for the treatment of CEP in people who require chronic or repeat courses of corticosteroids is an off label (unlicensed) use. Clinicians in Wales consider there is an unmet need and have identified a cohort of patients who could benefit from this treatment.

Current One Wales Interim Commissioning Decision

It is the view of the Interim Pathways Commissioning Group (IPCG) that mepolizumab (Nucala®) should not be supported within NHS Wales for the treatment of chronic eosinophilic pneumonia. December 2019.

Licence status

Mepolizumab (Nucala®) for chronic eosinophilic pneumonia remains an off-label indication.

Guidelines

There are no published guidelines for the treatment of chronic eosinophilic pneumonia.

Licensed alternative medicines/Health Technology Appraisal advice for alternative medicines

There are no new medicines or health technology appraisal advice.

Efficacy/Effectiveness

A repeat literature search conducted by AWTTC, together with conference abstracts identified by clinical experts, identified one open label retrospective study, two case studies of individual patients and seven conference abstracts of mepolizumab to treat CEP. These studies are briefly described below.

Open label multi-centre retrospective study:

Brenard et al. (2020) reports on 10 patients with idiopathic chronic eosinophilic pneumonia (ICEP)[3]. Patients from four academic centres and one regional hospital in Belgium were considered for inclusion. High-resolution computed tomography (HRCT) features were compatible with diagnosis (consolidative opacities). Patients with significant other organ involvement (skin, heart) were excluded. Outcomes of interest were annual rates of relapse, oral corticosteroid (OCS) use and lung lesions on HRCT. A relapse was defined as the recurrence of respiratory symptoms accompanied by increase in blood eosinophils, new lesions on the chest X-ray, or HRCT in the absence of infection. For the assessment of lung lesions the last available HRCT prior to mepolizumab treatment was compared to the first HRCT during follow-up (after starting mepolizumab). The final analysis included five women and five men, median age at diagnosis was 48 (range 22-65). Eight were non-smokers and two were former smokers. Four patients had a history of asthma and two developed asthma and airway hyper responsiveness concomitantly to ICEP. None of the patients had responded to prior immunosuppressive therapy other than OCS. At diagnosis median blood eosinophil was 2,035/microlitre (range, 720-22,860). Median time from diagnosis to mepolizumab treatment was 36.5 months (range, 12-129). During this time all patients experienced at least one relapse requiring OCS. Seven out of the 10 patients were still receiving OCS at the time of mepolizumab initiation (median dose was equivalent to 5 mg daily prednisone). At mepolizumab initiation median blood eosinophil count was 900/microlitre (range, 410-2,130). Six patients received 100 mg mepolizumab every four weeks (dose approved for severe asthma) and four patients received 300 mg every four weeks (similar to the dose used in studies for eosinophilic granulomatosis with polyangitis and hypereosinophilic syndromes). Median follow-up with mepolizumab treatment was nine months (range, 6-12 months). Mepolizumab was associated with a significant reduction in the annual rate of relapse from 0.8 to 0.0 ($p = 0.002$). Blood eosinophil count was significantly reduced after three months (median, 100/microlitre; range, 55-190). After six months eight patients underwent HRCT and 2 underwent a chest X-ray. Comparisons of pre and post mepolizumab HRCT demonstrated a complete disappearance of lung lesions in seven patients. A significant improvement with mild ground-glass opacities was observed for the remaining patient. Neither of the chest X-rays demonstrated any lung lesion. Four patients had HRCT at 12 months, none of these showed any residual lesion. During the first three months of mepolizumab

treatment daily OCS use dropped from 5 mg (range, 0-10) prednisone to 0 (range, 0-5) with only one patient still on OCS. After six months this patient was only taking 2.5 mg prednisone daily. No differences in characteristics nor circulating eosinophils were found between the two dosing subgroups at baseline, initiation of mepolizumab and during follow-up. No side effects related to mepolizumab treatment were reported in any patient[3].

Individual case studies:
Shimizu et al. (2020) reported a case of a woman with asthma diagnosed in 1997 at the age of 58 years with CEP[4]. She initially responded to a course of high dose oral prednisolone, deteriorated nine years later and was treated with inhaled corticosteroids and bronchodilators, and leukotriene antagonists. Her symptoms worsened over the years and she required regular oral prednisolone. She was started on 100 mg mepolizumab in June 2016 following a relapse of CEP. In July her blood eosinophil count had decreased. In October, her chest CT showed no infiltrative shadows and she successfully stopped daily use of oral prednisolone. In June 2017, she reduced her daily dose of inhaled budesonide/formoterol. In May 2018 she switched to 30 mg benralizumab (targets interleukin-5, like mepolizumab) every four weeks for the first three doses followed by fixed-dose injection every eight weeks to enable a longer dosing interval than mepolizumab. No adverse effects were observed[4].

Ciuffreda et al. (2020) reported a case of a 59-year-old non-smoking woman with past history of allergic asthma diagnosed in 2011 with CEP[5]. She was treated with oral steroids, bronchodilators, inhaled corticosteroids and a leukotriene antagonist. Attempts to reduce and suspend steroids were without success. In March 2019, the patient decided by herself to reduce and suspend the steroids because of adverse effects (hyperglycaemia, hypertension, osteoporosis and aesthetic changes [moon face]). A few weeks later a CT scan presented new ground-glass opacities and blood eosinophil count of 1,800/microlitre. The patient refused to restart steroids due to the adverse events she had experienced previously. Mepolizumab 100 mg every four weeks was started. Her symptoms gradually improved and a CT scan after 3 months showed disappearance of pulmonary infiltrates. After 10 months of treatment her lung function results were normal and there was a significant reduction in her blood eosinophil count to 8/microlitre[5].

Conference abstracts:
Askin and Sjulin (2020) reported a case of a 47-year-old African American woman who had a history of persistent productive cough and dyspnoea[6]. Further examination identified abnormalities on chest CT and an elevated eosinophil count. Steroid therapy for CEP was started which resulted in clinical improvement. Tapering below 20 mg/day was unsuccessful. Mepolizumab (dose not reported), resolved her symptoms and allowed cessation of all steroids[6].

Barash et al (2020) reported a case of a 71-year-old man with a history of recurrent cough and dyspnoea responsive to short courses of oral corticosteroids[7]. He had abnormalities on chest CT, the presence of alveolar infiltrates, bronchoalveolar lavage (BAL) eosinophilia (12%) but chronic low level peripheral eosinophilia. He was started on corticosteroids and this significantly reduced symptoms for six months but relapsed upon discontinuation. Steroid treatment was restarted but he developed psychiatric symptoms related to high dose corticosteroid use. Mepolizumab (dose not reported) was started. The patient demonstrated symptomatic and radiographic stability and neuropsychiatric disturbances were resolved[7].

Balasubramanyam et al (2019) reported a case of a 16-year-old girl who had a year long history of fever, cough, and shortness of breath[8]. She was initially diagnosed with asthma however further evaluation revealed elevated peripheral eosinophilia, abnormalities on chest CT and elevated eosinophils at BAL. She was diagnosed with ICEP and discharged on prednisone (10 mg daily) and mepolizumab (100 mg every 4 weeks). Treatment was unsuccessful and high-dose steroids were repeatedly required. This led to cushingoid features and she was also prescribed ciclosporin 3 mg/kg and hydroxyurea 500 mg twice daily. The patient was lost to follow-up[8].

Jithpratuck et al. (2019) reported a case of a 20 year old woman who had a history of asthma, environmental allergies, and eosinophilic oesophagitis presented with productive cough and progressive shortness of breath[9]. She had abnormalities on chest CT and elevated peripheral eosinophils. She was diagnosed with CEP and started on prednisone. She required a prolonged course of prednisone due to relapse of her respiratory symptoms while previously tapering steroids. Mepolizumab (dose not reported)

was started and within one month of treatment her respiratory symptoms and lung function improved. During one year of mepolizumab treatment, her respiratory symptoms remained stable, with no exacerbation or prednisone use[9].

McInnis et al. (2019) reported a case of a 47 year old woman who had a history of asthma and rhinosinusitis[10]. She had elevated eosinophils at BAL (90%), elevated serum eosinophils and abnormalities on chest CT. She was diagnosed with ICEP and started on prednisone 60 mg daily. She went on to relapse three times over several years. She was started on mepolizumab (100mg every 4 weeks) when the prednisone dose was at 5 mg daily during the third relapse. At time of publication she had continued mepolizumab, remaining clinically stable and free from corticosteroid treatment for more than 12 months[10].

Mendes et al. (2019) reported two cases. The first was a 54 year old woman, non-smoker, with history of allergic asthma, diagnosed with CEP and started on prednisolone 1 mg/kg daily[11]. Steroid tapering was unsuccessful and she required a long-term maintenance dose of 10 mg daily. The patient was started on mepolizumab (100 mg every 4 weeks). After eight weeks her respiratory symptoms had markedly improved, blood eosinophil had decreased and pulmonary function remained stable. Steroid dose was maintained due to *de novo* idiopathic thrombocytopenic purpura not attributed to mepolizumab[11].
The second case was a 21 year old woman with history of non-allergic asthma, diagnosed with CEP. She was a non-smoker and started on prednisolone 0.6 mg/kg daily. Steroid discontinuation was unsuccessful and she required a long-term maintenance dose of 10 mg daily. Mepolizumab was started (300 mg every 4 weeks) and after eight weeks respiratory symptoms were controlled and steroid dose was gradually reduced to 5 mg on alternate days[11].

Wolff et al. (2019) reported a case of a 45-year-old serviceman who had a two year history of respiratory distress with cough, dyspnoea, and recurrent pneumonia[12]. He was an ex-smoker. He had abnormalities on chest CT, elevated immunoglobulin E and peripheral eosinophilia and was diagnosed with CEP, allergic asthma, and rhinosinusitis in 2008. During 12 months of daily corticosteroid treatment, he had persistent eosinophilia and disabling respiratory symptoms. Treatment with mepolizumab (dose not reported) was started. In 2012 he stopped working in austere overseas environments. His chest CT scan showed resolution of symptoms, but he continued to require treatment for frequent asthma exacerbations[12].

Safety
No relevant safety analyses were identified in the repeat literature search.

Cost effectiveness
No relevant cost-effectiveness analyses were identified in the repeat literature search.

Budget impact
The estimated eligible population reported in the ESR was 35 patients per annum in Wales. Since November 2019 there have been no IPFR requests made for this medicine and indication across Wales.

Welsh commercial access agreement
This medicine is currently not licensed for the indication under consideration (i.e. off-label) and therefore as the Pharmaceutical Industry's code of practice prevents a company from promoting an off-label use of a medicine, a commercial agreement cannot be offered by the company.

Impact on health and social care services
No new impact data provided, though the impact of this medicine is considered to be minimal. Clinicians remain supportive of the use of mepolizumab in CEP patients.

Patient outcome data
It would appear that no patients in Wales have received mepolizumab for CEP.

References

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