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Severe Eosinophilic Asthma

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About the Reviewers

Dr Jeffrey Garrett
Clinical Associate Professor, Respiratory Medicine
MBChB (Otago), FRACP, FThorSoc

Associate Professor Jeffrey Garrett is a specialist respiratory physician. He was Clinical Director of Medicine at Middlemore Hospital between 2002 and 2015, and Clinical Director of Respiratory Services at Greenlane Hospital between 1992 and 2000. He has been an active researcher, predominantly in asthma, for more than 20 years with 75 publications in international journals. He is currently involved in transforming electronic healthcare models in asthma and COPD into care and evaluating the use of biomarkers to direct asthma and COPD care more accurately. He was made a Fellow of the Thoracic Society of Australia and New Zealand in March 2019.

Dr Anthony Jordan
BHB, MBChB, FRACP

Dr Anthony Jordan is a Specialist in Internal Medicine (Clinical Immunologist, Allergist and General Physician) and Service Clinical Director for Ambulatory Services working at Auckland City Hospital. Anthony is also honorary Senior Lecturer in the Department of Medicine at the University of Auckland.

This publication is intended as an educational resource for healthcare professionals, particularly those involved in the assessment and management of patients with severe asthma. It discusses the pathophysiology and burden of severe asthma, with a focus on the eosinophilic phenotype. It reviews strategies for assessment and management of severe eosinophilic asthma, in particular the role of anti-IL-5 therapy. The publication has been commissioned by GlaxoSmithKline NZ Limited.

Introduction

The development of monoclonal antibodies targeting the type 2 inflammation pathway in patients with severe asthma has led to the recognition of an eosinophilic phenotype.[1,2] This phenotype is characterised by high eosinophil levels in induced sputum and peripheral blood, and is associated with frequent asthma exacerbations.[1,2] Patients with severe asthma, including eosinophilic asthma, have a high disease burden[3-6] and decreased health-related quality of life,[7] despite guideline-directed treatment with maximum dose inhaled corticosteroids and controller medications. Reducing the need for oral corticosteroids is an important management goal in these patients.[8,9]

Monoclonal antibodies targeted against interleukin (IL)-5, the major cytokine responsible for the differentiation, maturation, activation and survival of eosinophils,[10] are now available for the add-on treatment of severe eosinophilic asthma, and have been included in Global Initiative for Asthma (GINA) guidelines for asthma management.[8,9] Mepolizumab was the first anti-IL-5 agent to receive approval from the US Food and Drug Administration[11] and as of mid-2019 was the only anti-IL-5 agent registered for use in New Zealand.[12]

Inflammatory mechanisms in severe asthma

Inflammatory mechanisms in asthma can be categorised as type 2 and non-type 2 (**see Figure 1**).[2] A number of cytokines are involved in type 2 inflammation, including IL-4, IL-5, IL-13, and these are most commonly produced by the adaptive immune system on recognition of allergens.[2] Type 2 inflammation is frequently characterised by eosinophils, and may be accompanied by atopy, whereas non-type 2 inflammation is often characterised by neutrophils.[2] In mild-to-moderate asthma, type 2 inflammation usually improves rapidly when inhaled corticosteroids are taken regularly and with good inhaler technique.[2] In the context of severe asthma, the type 2 phenotype is characterised by persistent inflammation despite regular, correct use of high-dose inhaled corticosteroids.[2] Type 2 asthma can be further classified as allergic or eosinophilic disease.[13]

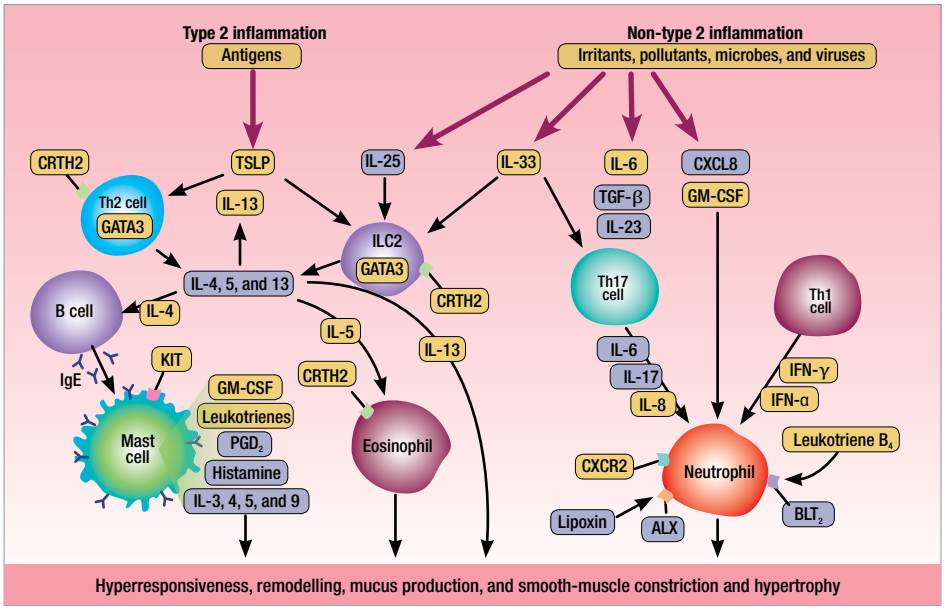

Figure 1. Inflammatory mechanisms of severe asthma (adapted from Israel E & Reddel HK. N Engl J Med. 2017 Sep 7;377(10):965-976).[2]

Eosinophils are largely, but not exclusively, regulated by IL-5.[10] IL-5 is important in the differentiation, maturation, activation and survival of the eosinophil.[10] The cytokine acts upon the eosinophil cell surface receptor to release granular proteins, lipid mediators and growth factors.[10] In this way IL-5 can influence airway injury, airway responsiveness and airway remodelling.[10]

Prevalence of severe eosinophilic asthma

Eosinophilic asthma occurs in approximately 30-50% of patients with severe asthma.[14,15] In New Zealand, a recent cohort study has estimated the prevalence of severe eosinophilic asthma at 6.2% of all asthma cases, when defined as ≥2 exacerbations in the previous year despite inhaled corticosteroid prescription above the medium dose plus a controller medication, and a blood eosinophil count ≥0.3 x 10^9 cells/L (≥300 cells/μL) in the previous year or ≥0.15 x 10^9 cells/L (≥150 cells/μL) in the past 6 weeks.[16] In the study, prevalence of severe eosinophilic asthma was highest in patients of Māori ethnicity (9.4%), those aged 60-69 years (9.3%) and former smokers (8%).[16]

Burden of severe asthma

Severe asthma accounts for the highest burden in patients with asthma, in terms of greater healthcare resource use, as well as time off work and school.[3,4] In a large-scale analysis of patients with asthma in the UK and US, asthma-related hospital readmission rates and costs approximately doubled between GINA Step 1 and 5 and in patients with ≥2 versus <2 exacerbations in the previous year.[5]

The negative impact of severe asthma on workplace productivity has been highlighted in an analysis from the Severe Asthma Web-based Database, an observational registry managed by the Australasian Severe Asthma Network with centres in Australia, New Zealand and Singapore.[17] In patients aged 30-50 years, only 69% of those with severe asthma were employed, compared with 100% of those with non-severe asthma.[17] Presenteeism (self-reported impairment at work) and impairment in daily activities outside work were more frequent in patients with severe vs non-severe asthma and in those with poorer asthma control, poorer lung function and more exacerbations in the past year.[17] In patients with severe asthma, presenteeism was more common in those with poorer asthma control, poorer asthma-related quality of life and symptoms of depression or anxiety.[17]

Another Australian study showed the long-term, debilitating burden of severe asthma, suggesting it should be considered differently to milder disease.[6] In-depth, semi-structured interviews of patients revealed significant emotional distress as a result of the symptoms, treatment (particularly oral corticosteroid treatment), and limitations imposed by their disease.[6]

Long-term use of oral corticosteroids in patients with severe asthma is associated with serious adverse effects, including obesity, diabetes, osteoporosis, cataracts, hypertension, adrenal suppression and psychiatric disturbances.[18] Even short-term use is associated with sleep disturbance and an increased risk of infection, fracture and thromboembolism.[19] Reducing the need for oral corticosteroids is therefore a high priority in the management of severe asthma.[8,9]

Healthcare resource use in patients with eosinophilic asthma

A number of studies have reported higher healthcare resource utilisation in patients with eosinophilic asthma compared with other asthma patients. In a New Zealand cohort study, healthcare resource utilisation was 70% higher and annual healthcare costs were 3.4 times higher in patients with severe eosinophilic asthma compared with other asthma patients.[16] Similar findings were noted in a large cohort study from the UK, with healthcare resource use and costs 4 times higher in patients with severe, uncontrolled eosinophilic asthma compared with the general asthma population.[20]

A US study found that uncontrolled asthma patients with blood eosinophil counts >0.4 x 10^9 cells/L in the previous 12 months were associated with 4.5 times greater costs for outpatient services and emergency department visits at baseline vs patients with controlled asthma.[21] After their first observed asthma visit, patients with uncontrolled eosinophilic asthma had higher utilisation of inpatient, outpatient, emergency department and pharmacy services than those with controlled asthma, with 1.7 times greater costs.[21]

In a Finnish observational study, asthma-related resource utilisation was compared for asthma patients with blood eosinophil counts ≤0.3 x 10^9 cells/L vs >0.3 x 10^9 cells/L.[22] Comorbidities such as pneumonia, sinusitis and nasal polyps were more common in patients with blood eosinophils >0.3 x 10^9 cells/L vs those with lower counts.[22] Hospital admissions and outpatient visits were more frequent in those with blood eosinophils >0.3 vs ≤0.3 x 10^9 cells/L.[22]

Severe asthma and quality of life

Severe asthma has a significant impact on health-related quality of life.[7] A UK study of patients with moderate to severe asthma assessed the impact of exacerbations on health-related quality of life.[23] All measures were significantly worse for patients who experienced exacerbations compared with those who did not.[23] Similarly, an analysis of the US TENOR study including patients with severe or difficult-to-treat asthma found that greater severity and numbers of asthma exacerbations within 12 months of follow-up were significantly associated with decreased asthma-related quality of life.[24]

EXPERT COMMENT: ASSOCIATE PROFESSOR JEFFREY GARRETT

Severe asthma is a particular problem in New Zealand, with a disturbing and ongoing inequality in health outcomes between ethnic and socioeconomic groups.[25] In an audit of 465 adult patients referred to the Middlemore Hospital outpatient clinic in 2012-13, 305 fulfilled the criteria for uncontrolled asthma. The majority were poorly controlled due to non-adherence, poor inhaler technique, inadequate inhaled corticosteroid dose or comorbidities, but 34 fulfilled the criteria for treatment-resistant asthma, of whom 50% had blood eosinophil levels >0.3 x 10^9 cells/L. All 34 patients had impaired quality of life. Only 30% were still working due to the negative impact of asthma. Thirteen patients are registered with the Severe Asthma Web-Based Database of the Australasian Severe Asthma Network. Extrapolated across the entire New Zealand population, there are likely to be around 200 patients under outpatient clinic care who would currently fulfil criteria for treatment with monoclonal antibody therapies once current asthma therapy and care has been maximised.

EXPERT COMMENT: DR ANTHONY JORDAN

We have seen and celebrated since the late 1980s a marked and progressive reduction in asthma morbidity and mortality rates. New Zealand has taken an active role globally and locally to address inadequacies in health systems and treatment paradigms that contributed to this. However, globally in the last decade data would suggest that we have plateaued in our efforts to reduce mortality in asthma.[26] To make further headway in this area we need to re-examine our conventional approaches to asthma management, recognise the complex patient characteristics, their lifestyles, and structural barriers that do not respond to a single disease-based approach – only then can we say we are practicing precision medicine.

ABOUT RESEARCH REVIEW

Research Review is an independent medical publishing organisation producing electronic publications in a wide variety of specialist areas. Research Review publications are intended for New Zealand medical professionals.

Educational Series are a summary of the most important international and local literature which impacts on treatment of a specific medical condition. These Reviews provide information on a disease, current treatment and local /international guidelines. They are intended as an educational tool. Publications are free to receive for health care professionals, keeping them up to date with their chosen clinical area.

Treatable traits and the rationale for anti-IL-5 therapy

The therapeutic role of anti-IL-5 agents in asthma was first postulated in the early 2000s when an animal study showed eosinophilic reduction in bronchoalveolar lavage and lung tissue, and reduction of airway responsiveness, after treatment with an anti-IL-5 monoclonal antibody.[27,28] In 2009, small randomised controlled studies by Haldar et al. and Nair et al. first demonstrated the efficacy of the anti-IL-5 monoclonal antibody mepolizumab in patients with eosinophilic asthma, showing a reduction in exacerbations and corticosteroid-sparing effects.[29,30]

The introduction of treatments targeting the type 2 inflammation pathway in asthma, including anti-IL-5 agents, marks a change in approach to the pharmacological management of asthma.[1,31] Historically, treatment has been based on disease control and severity, with no recognition of the heterogeneous nature of asthma.[1,31] Specific asthma phenotypes are now recognised, giving rise to the concept of treatable traits.[1,31] Eosinophilic airway inflammation is an important treatable trait that can be targeted with anti-IL-5 therapy.[1,31]

Mepolizumab was the first anti-IL-5 agent to receive approval from the US Food and Drug Administration as an add-on treatment for patients with severe eosinophilic asthma,[11] and its efficacy and safety has been confirmed in a number of phase 3 trials. These include the DREAM trial, a dose-ranging study of intravenous mepolizumab,[32] MENSA and SIRIUS, which were the confirmatory trials used for registration of subcutaneous mepolizumab,[33,34] the MUSCA trial of health-related quality of life,[35] and the open-label extension studies COSMOS and COLUMBA.[36,37] Key outcomes from these trials were:

- Mepolizumab reduced clinically significant asthma exacerbations by 53% vs placebo[33]
- Mepolizumab allowed a median 50% reduction in oral corticosteroid dose[34]
- Mepolizumab produced early and sustained improvements in health-related quality of life[35]
- Mepolizumab was well tolerated, with overall rates of adverse events comparable to those with placebo, albeit higher rates of injection site reactions[33]
- Clinical effectiveness of mepolizumab was maintained for up to 4.5 years, with a similar tolerability profile to short-term use.[36,37]

A meta-analysis of four clinical trials of mepolizumab, including DREAM, MENSA and SIRIUS, found that mepolizumab approximately halved the rate of asthma exacerbations requiring hospitalisation and/or emergency room visits compared with placebo in patients with severe eosinophilic asthma.[38]

A 2017 Cochrane review supported the use of anti-IL-5 agents as an adjunct to standard of care in patients with severe eosinophilic asthma.[39] Anti-IL-5 agents have been included in Step 5 of the GINA guidelines as add-on therapy for severe eosinophilic asthma.[8,9]

EXPERT COMMENT: ASSOCIATE PROFESSOR JEFFREY GARRETT

Severe asthma is a complex, multifactorial disorder that requires specialist multidisciplinary input for optimal clinical outcomes. Following multidimensional assessment for optimisation of current therapy, self-management skills and comorbidities, all patients should be accurately phenotyped. Those found to have eosinophil levels >0.5 x 10^9 cells/L at any time in the previous 6 weeks, who have required more than 4 courses of oral corticosteroids or continuous corticosteroids, or who have required emergency department attendance or hospitalisation and have severe symptoms evaluated by either the Asthma Control Test or Asthma Control Questionnaire, are potentially amenable to mepolizumab treatment using criteria suggested by the Respiratory Advisory Group to Pharmac. I personally have used blood eosinophil levels of >0.4 x 10^9 cells/L and/or eosinophil levels of >3% on induced sputum to identify presence of eosinophilic inflammation and to exclude non-type 2 neutrophilic or paucigranulocytic patients. As shown in **Figure 1**, there are two pathways which lead to eosinophilic airway inflammation: Th2 (atopic) or ILC2 (late onset/non atopic). IL-5 and IL-13 are important cytokines for both pathways, and thus anti-IL-5 agents are a very attractive concept. Whilst omalizumab remains an alternative, only 10 of the 34 patients with treatment-resistant asthma in the 2012-2013 Middlemore Hospital outpatient clinic audit fulfilled Pharmac criteria for this drug, of whom 3 have failed therapy. The majority of the remaining patients would be amenable to treatment with anti-IL-5 or anti-IL-13 agents.

EXPERT COMMENT: DR ANTHONY JORDAN

We have seen a significant shift in the recent GINA guidelines for asthma management,[8] recognising that short-term symptom relief alone is not adequate in our patients. This approach leaves them exposed to the risk of further exacerbations. We have known for a long time that asthma is an inflammatory disorder, and the advent and use of inhaled corticosteroids marked a huge leap forward in the treatment of asthma. In those patients who have true treatment-resistant asthma despite all available inhaled and oral therapies, we have needed further targeted therapies addressing this underlying inflammatory process. As an anti-IL-5 agent, mepolizumab targets those patients with eosinophilic-driven asthma, and in this group blood eosinophils are the most predictive biomarker of response. A modelling analysis of data from the DREAM and MENSA studies tells us that even in patients with a baseline eosinophil count of 0.15 x 10^9 cells/L there is a meaningful reduction in asthma exacerbations (30% in DREAM and 39% in MENSA), and that reduction increases when extrapolated out to higher eosinophil levels.[45]

Assessment of severe asthma phenotype

The GINA Global Strategy for Asthma Management and Prevention,[8] and a separate GINA guide for Difficult-to-Treat and Severe Asthma,[9] outline steps for the assessment and management of patients with severe asthma – that is "*patients with persistent asthma symptoms or exacerbations despite correct inhaler technique and good adherence with GINA Step 4 treatment and in whom controller options have been considered*".[8,9] Such patients should be referred to a specialist with expertise in the management of severe asthma, and may benefit from phenotype-guided add-on treatment.[8,9]

The severe asthma phenotype should be assessed during high-dose inhaled corticosteroid treatment.[9] As oral corticosteroids rapidly reduce markers of type 2 inflammation, assessment should be made before starting oral corticosteroids, or during treatment with the lowest possible dose.[9] A recent report suggests that blood eosinophil count should be measured 4-8 weeks after a severe asthma exacerbation, to avoid the confounding effect of oral corticosteroid treatment.[40] Blood eosinophil and exhaled nitric oxide (FeNO) counts can be repeated up to 3 times before assuming asthma is non-type 2.[9]

The possibility of refractory type 2 inflammation should be considered if any of the following are found while the patient is taking high-dose inhaled corticosteroids:

- Blood eosinophils ≥0.15 x 10^9 cells/L
- FeNO ≥20 ppb
- Sputum eosinophils ≥2%
- Asthma is clinically allergen-driven.[9]

Non-biologic options for patients with type 2 inflammation

Before moving to treatment with biologic agents for patients with type 2 inflammation, it is suggested that adherence with current asthma treatments is assessed objectively.[9] This could be via monitoring dispensing records, blood prednisone levels or electronic inhaler monitoring.[9]

Clinical type 2 phenotypes for which specific, non-biologic add-on treatment is available should also be considered (see **Table 1**).[9]

Clinical type 2 phenotype	Non-biologic add-on treatment
Aspirin-exacerbated respiratory disease	Leukotriene modifier ± aspirin desensitisation
Allergic bronchopulmonary aspergillosis	Oral corticosteroid ± antifungal
Chronic rhinosinusitits and/or nasal polyposis	Intensive intranasal corticosteroid

Table 1. Clinical type 2 phenotypes for which non-biologic add-on treatment is available.[9]

Biologic options for type 2 inflammation

In order to determine which biologic treatment is appropriate for severe asthma with type 2 inflammation, the predominant phenotype (allergic or eosinophilic) must be found.[41] **Table 2** shows the clinical features and biomarkers which can be used to differentiate between eosinophilic and allergic asthma.[41] Omalizumab is the add-on treatment of choice for patients with severe allergic asthma, while anti-IL-5 agents are suitable for those with severe eosinophilic asthma.[9,41]

Eosinophilic asthma	Allergic asthma
Late onset	Early onset
Negative skin prick/RAST test with no clinically significant allergies	Positive skin prick/RAST test with clinically significant allergies
IgE <100 IU/ml	IgE >100 IU/ml
Nasal polyps	Allergic rhinitis
Very high FeNO (>50 ppb)	High FeNO (30-50 bbp)
Blood eosinophils >0.3 x 10^9 cells/L	Blood eosinophils <0.3 x 10^9 cells/L

Table 2. Clinical features and biomarkers of eosinophilic and allergic asthma.[41]
FeNO, exhaled nitric oxide; IgE, immunoglobulin E; RAST, radioallergosorbent.

Omalizumab

Omalizumab is approved in New Zealand for the treatment of patients with severe persistent allergic asthma and immunoglobulin E levels ≥30 IU/ml, a positive skin test or *in vitro* reactivity to a perennial aeroallergen, and inadequate symptom control on inhaled corticosteroids.[42]

Mepolizumab

In New Zealand, mepolizumab is currently the only anti-IL-5 agent approved for the treatment of severe eosinophilic asthma.[12] In registration trials of mepolizumab, criteria for treatment included a blood eosinophil count of ≥0.15 x 10^9 cells/L at screening or ≥0.3 x 10^9 cells/L in the past year, and ≥2 exacerbations in the previous year treated with oral corticosteroids or maintenance treatment with oral corticosteroids, in addition to regular inhaled corticosteroids and controller asthma medication.[33,34] A single measurement has been shown to identify a blood eosinophil count of ≥0.15 x 10^9 cells/L in approximately 85% of patients.[43] Blood eosinophil count also correctly predicts sputum eosinophilia, and is a more practical measurement for routine clinical use.[43]

In patients with an overlapping phenotype, the physician may choose whether to start treatment with mepolizumab or omalizumab, as no direct comparison has been made between these agents.[41] However mepolizumab could be considered as a first-choice treatment in patients dependent on oral corticosteroids, based on the corticosteroid-sparing effects of this agent.[34,41]

EXPERT COMMENT: ASSOCIATE PROFESSOR JEFFREY GARRETT

There has been a move away from initiation of asthma treatment with short-acting bronchodilators to using inhaled corticosteroids instead. This is in acknowledgement that asthma is an inflammatory disorder. If good control is not easily achieved, there is a need to ensure inhaler type and inhaler technique have been optimised, and that patients are adherent with therapy. The use of biomarkers, including straightforward blood eosinophil counts (as outlined in this article), as well as spirometry has allowed treatment to become more precise and more personalised. If patients remain symptomatic despite optimisation of therapy, then referral to a specialist or specialty clinic is indicated. We are evolving to develop a Severe Asthma Clinic to more accurately phenotype patients with severe asthma.

Whilst we are better utilising the skills of our subspecialty colleagues (eg: gastroenterologists to assess severity of gastro-oesophageal reflux, otorhinolaryngologists to assess upper airways more carefully and metabolic units and/or bariatric surgeons to co-manage obesity-related asthma), we remain hampered in New Zealand by poor access to monoclonal antibody therapy and to new proven therapies such as thermoplasty. Until 2018, the anti-IgE monoclonal antibody omalizumab was restricted by Pharmac for use in patients who had both eosinophilic asthma and frequent hospitalisation. However, we have noted that 86% of asthmatics with frequent asthma admissions are poorly adherent with therapy and very few fulfilled the criteria for severe refractory asthma. These restrictive criteria have just been lifted, but we are only able to prescribe omalizumab to patients with an IgE level between 76 and 1300 IU/ml. Of the current patients in our clinic with severe refractory eosinophilic asthma, 34% have an IgE level >1300 IU/ml and 42% <76 IU/ml. Since patients with an IgE level >1300 IU/ml are equally likely to respond to omalizumab, we either need to broaden the criteria or introduce mepolizumab. Ideally, we need to do both.

EXPERT COMMENT: DR ANTHONY JORDAN

If you reach step 5 of the GINA management guidelines for asthma it is suggested that you are referred for phenotypic assessment of your asthma to guide further treatment.[8] Here lies a significant inequity issue, to facilitate this we desperately need to ensure that all our patients have access to a Severe Asthma Clinic. This allows us to address non-asthmatic conditions that may be mimicking severe asthma (12-30% of patients), ensure adherence, utilise non-medication based interventions and to add on and monitor the response to treatments which have significant cost and/or potentially long-term side effects if not utilised correctly. At present for eosinophilic-driven disease, we are able to use oral corticosteroids, with their associated long-term side effects, and omalizumab, a fortnightly subcutaneous injected therapy for those with allergic asthma who fit a tight clinical criteria that limits overall utility. Mepolizumab would allow us to treat a broader range of patients with high blood eosinophils across both allergic and non-allergic phenotypes.

Management of severe eosinophilic asthma

GINA guidelines suggest a trial with an anti-IL-5 agent for ≥4 months in patients with severe eosinophilic asthma.[9] Response to treatment should include consideration of symptom control and exacerbations, treatment intensity, lung function, adverse events and patient satisfaction.[9]

In patients showing a good response, advice is to re-evaluate the need for each treatment every 3-6 months, including the anti-IL-5 agent.[9] In patients with an equivocal response to an initial trial with an anti-IL-5 agent, the trial could be extended to 6-12 months.[9] If there is no response after this time, anti-IL-5 treatment should be stopped, and the role of eosinophilic airway inflammation in the pathogenesis of the patient's asthma re-evaluated.[9] Other factors which should be considered at this time include differential diagnosis, inhaler technique, adherence, comorbidities, side effects and emotional support.[9]

Official criteria for assessment of treatment response with anti-IL-5 agents have yet to be defined. However, based on clinical trial data,[33,34] 2017 recommendations from the UK National Institute for Health and Care Excellence define response to mepolizumab as a ≥50% reduction in exacerbation rate or a clinically significant reduced dose of continuous oral corticosteroids.[44]

Predictors of response to anti-IL-5 agents

The main factors predictive of a good response to anti-IL-5 therapy are higher baseline blood eosinophil count and a higher number of severe exacerbations in the previous year.[9]

In the MENSA trial, the rate of clinically significant exacerbations was reduced by 79% in mepolizumab-treated patients with a blood eosinophil count ≥0.5 x 10^9 cells/L at baseline, compared with 53% in the overall mepolizumab-treated group.[33] Improvements in lung function and asthma control were also proportionally greater in those with eosinophils ≥0.5 x 10^9 cells/L.[33] In the DREAM trial, baseline eosinophil count was also associated with treatment response to mepolizumab.[32] An analysis of data from both trials highlighted the close relationship between baseline blood eosinophil count and efficacy of mepolizumab in patients with severe eosinophilic asthma and a history of exacerbations.[45]

A cluster analysis of data from the DREAM study examined patient characteristics associated with a greater response to mepolizumab.[46] While blood eosinophil count was the biomarker of choice for predicting response to mepolizumab, the largest response was seen in patients with a high blood eosinophil count, airway reversibility, obesity, and more comorbidities.[46]

However, it is important to note that even patients with a baseline blood eosinophil count of 0.15 x 10^9 cells/L have a clinically relevant reduction in exacerbation rate (39% reduction in the MENSA study).[43,45]

Influence of previous treatment and background controller medications

Patients with severe eosinophilic asthma respond positively to mepolizumab, regardless of previous treatment with omalizumab, according to a post-hoc analysis of data from the MENSA and SIRIUS trials.[47] In MENSA, the exacerbation rate was reduced by 57% in patients with prior omalizumab use vs 47% in those with no prior omalizumab use.[47] Reductions in oral corticosteroid use and exacerbation rate in SIRIUS were comparable regardless of prior omalizumab use.[47]

Furthermore, the number or type of background controller therapies taken by patients does not impact on the effectiveness of mepolizumab.[48] In another analysis of MENSA trial data, clinically relevant reductions in exacerbations with mepolizumab vs placebo were seen in patients receiving inhaled corticosteroids plus 1, 2 or ≥3 controller therapies.[48] The largest reduction (63% decrease) was seen in those receiving ≥3 controller therapies, which represented patients likely to have the greatest burden of disease.[48] Mepolizumab was effective regardless of the type of controller medication used in addition to inhaled corticosteroids, including long-acting β-agonists (LABA) alone, LABA + additional agents excluding tiotropium, LABA + tiotropium and LABA + tiotropium + additional agents.[48]

Treatment withdrawal

GINA guidelines recommend that in patients with a good response to anti-IL-5 agents, a gradual decrease or stopping of oral corticosteroids should be considered first, because of the significant adverse effects of these agents.[9] A reduction in the dose of inhaled corticosteroids can be considered after 3-6 months, but these should not be completely stopped.[9] Current consensus advice is to continue at least medium dose inhaled corticosteroids.[9]

For anti-IL-5 agents, GINA guidelines state that a trial of withdrawal may be considered if, after ≥12 months of treatment, asthma remains well-controlled on medium dose inhaled corticosteroids.[9] However, studies of withdrawal of anti-IL-5 agents are limited.[9] In a follow-up analysis of patients with refractory eosinophilic asthma treated with mepolizumab for 12 months, blood eosinophil count reverted to baseline 6 months after treatment cessation, and exacerbation frequency was significantly increased at 12 months.[49]

Potential continuation rules

A post-hoc analysis of data from the DREAM and MENSA trials found no evidence of a reliable rule predicting long-term reduction in asthma exacerbations with mepolizumab.[50] Potential continuation rules were investigated 16 weeks after treatment initiation.[50] Patients not meeting rules based on physician-rated response to treatment, lung function and asthma control still derived long-term benefit from mepolizumab.[50] Nearly all patients in whom mepolizumab failed to decrease blood eosinophils had a count of ≤0.15 x 10^9 cells/L at baseline.[50] Assessment of exacerbation reduction at 16 weeks was deemed premature for the prediction of long-term reduction.[50] The study authors concluded that initiation criteria for mepolizumab provide the best method of assessing patient benefit from mepolizumab, and that decisions about treatment continuation should be based on achieving a predefined reduction in longer term exacerbation frequency and/or oral corticosteroid dose.[50]

EXPERT COMMENT: ASSOCIATE PROFESSOR JEFFREY GARRETT

The majority of our severe, treatment-resistant asthmatics have an elevated eosinophil count >0.3 x 10^9 cells/L and have Asthma Control Tests indicating poor control. A small group have neutrophilic asthma with overlap syndrome (fixed airways obstruction) and have benefited from macrolide antibiotics. Another small group have mixed eosinophilic and neutrophilic inflammation. Together with the pure eosinophilic group this subgroup would benefit most from mepolizumab. The great majority have either relatively frequent exacerbations of asthma or are on continuous corticosteroids. If mepolizumab were available, it would be reasonable to review treatment effects after 3-6 months. However, in our experience whilst the majority improve immediately there is a subgroup who will exacerbate despite mepolizumab and undoubtedly because they have severe inflammation, bronchial hyper-responsiveness or fixed airways obstruction. Particularly during the early stages of treatment, they will remain susceptible to viral-induced exacerbations. I think it would be reasonable to consider continuing mepolizumab for 2 years and with a subsequent trial off therapy. The criteria for continuing treatment would need to be reviewed.

TAKE-HOME MESSAGES

- Severe eosinophilic asthma occurs in approximately 30-50% of patients with severe asthma[14,15]
- Severe asthma, including eosinophilic asthma, carries a high disease burden and significantly impacts health-related quality of life[3-7]
- Reducing the need for oral corticosteroids is a high priority in the management of severe asthma[8,9]
- Eosinophilic airway inflammation is an important treatable trait in severe asthma that can be targeted with anti-IL-5 therapy[1,31]
- The anti-IL-5 agent mepolizumab is approved in New Zealand as an add-on treatment for severe refractory eosinophilic asthma[12]
- Higher baseline eosinophil count and higher number of severe asthma exacerbations are the best predictors of a good response to anti-IL-5 therapy.[9]

EXPERT CONCLUSIONS: ASSOCIATE PROFESSOR JEFFREY GARRETT

New Zealand should support the establishment of Severe Asthma Clinics with multidisciplinary team input. Ideally, we should establish and maintain a severe asthma database to monitor patients' progress and demand systematic collection of data on patients who receive mepolizumab. At Middlemore Hospital, we have established a Day Centre to implement and monitor the first 3 injections of mepolizumab. We then transfer patients to their GP, with education on administration of the drug. We continue 3-monthly follow ups and monitor patients' progress through a dynamic pathway. We believe that this approach could easily be transferred to other District Health Boards.

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