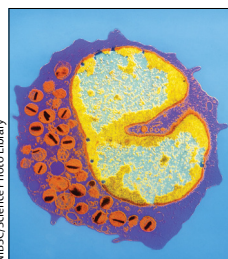


Mepolizumab, quality of life, and severe eosinophilic asthma



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It has been 2 years since mepolizumab, a first-in-class anti-interleukin-5 biological drug, was approved in Europe, Canada, USA, and other countries as an add-on treatment to standard of care for severe eosinophilic asthma. In *The Lancet Respiratory Medicine*, Geoffrey Chupp and colleagues¹ report the findings from their phase 3b study (MUSCA), which focused on health-related quality of life, and adds to the increasing evidence base of clinical efficacy for mepolizumab in severe eosinophilic asthma²⁻⁸ (table).

MUSCA was a placebo-controlled, randomised, double-blind, parallel-group, multicentre study undertaken in 146 hospitals or research centres in 19 countries. Eligible participants were patients with severe eosinophilic asthma (a blood eosinophil count of either ≥ 150 cells per μL at screening or ≥ 300 cells per μL during the past year) and a history of at least two exacerbations requiring treatment in the previous year despite regular use of high-dose inhaled corticosteroids plus other controller(s). Participants were randomly assigned (1:1) to a subcutaneous injection of mepolizumab 100 mg or placebo every 4 weeks for 24 weeks (final dose given at week 20). The primary endpoint was the mean change from

baseline in the St George's Respiratory Questionnaire (SGRQ) total score at week 24.

274 participants were assigned to mepolizumab, 277 to placebo. At week 24, mepolizumab improved SGRQ total score compared with placebo (least squares mean [SE] change from baseline -15.6 (1.0) vs -7.9 (1.0), a treatment difference of -7.7 (95% CI -10.5 to -4.9 ; $p < 0.0001$)—approximately double the previously defined minimally clinically important difference (MCID),⁹ and similar to the estimate of treatment effect on this measure in the phase 3 MENSA⁸ trial. Chupp and colleagues' study¹ extended these earlier findings and showed that reductions in SGRQ occurred as early as week 4, and that the dominant effect of treatment was on the symptom domain of the SGRQ. Collectively, the results suggest that the SGRQ is a more responsive measure than other more traditional measures of symptoms and quality of life (QOL) in asthma including the Asthma Control Questionnaire (ACQ) and the Asthma Quality of Life Questionnaire (AQLQ), both of which improve by less than the MCID (table).

A probable explanation for the differential responsiveness of these QOL measures is that the symptom domain of the SGRQ better identifies morbidity resulting from inflammation-related events such as mucus plugging,

	Patient population	Injected dose of mepolizumab	Exacerbation reduction (%)	Increase in pre-bronchodilator FEV ₁ (mL)	Reduction in ACQ5 scores	Increase in AQLQ scores	Reduction in SGRQ total score
Flood-Page et al ⁵	Moderate to severe asthma. No selection on inflammation or exacerbations	250 to 750 mg every 4 weeks for 12 weeks	..	-40 (-150 to 60) to -50 (-160 to 60)	..	..	..
Halder et al ²	>2 exacerbations per year. Sputum eosinophil count >3% in past year	750 mg intravenously every 4 weeks for 50 weeks	43% (8 to 68)	-50* (-260 to 150)	-0.04 (0.38 to -0.46)	0.35 (0.08 to 0.63)	..
DREAM ⁶	≥ 2 exacerbations per year ≥ 1 of the following in past year: fraction of exhaled nitric oxide >50 ppb; sputum eosinophil count >3%; blood eosinophil count >300 cells per μL ; prompt deterioration after 25% reduction in corticosteroid dose	75 to 250 mg or 750 mg intravenously every 4 weeks for 52 weeks	39% (19 to 54) to 52% (36 to 64) for three doses	56 (-43 to 155) to 81 (-19 to 180)	0.16 (-0.07 to 0.39) to 0.27 (-0.04 to 0.51)	0.05 (-0.19 to 0.29) to 0.22 (-0.02 to 0.46)	..
MENSA ⁸	≥ 2 exacerbations per year. Blood eosinophil count >150 cells per μL at screening or >300 cells per μL in past year	75 mg intravenously or 100 mg subcutaneously every 4 weeks for 32 weeks	47% (29 to 61) to 53% (37 to 65) for two doses	98 (11 to 184) to 100 (13 to 187)	0.42 (0.23 to 0.61) to 0.44 (0.25 to 0.63)	..	6.4 (3.2 to 9.7) to 7.0 (3.8 to 10.2)
MUSCA ¹	2 or more exacerbations/year Blood eosinophil count ≥ 150 cells per μL at screening or ≥ 300 cells per μL in past year	100 mg subcutaneously every 4 weeks for 24 weeks	58% (44 to 69)	120 (47 to 192)	0.40 (0.22 to 0.58)	..	7.7 (4.9 to 10.5)

ACQ5=five item Asthma Control Questionnaire. AQLQ=Asthma Quality of Life Questionnaire. SGRQ=St George's Respiratory Questionnaire. ppb=parts per billion. ..=data not available. *Post-bronchodilator value.

Table: Summary of main outcomes of trials of mepolizumab in patients with asthma

airway wall oedema, and structural airway changes than does the ACQ and AQLQ, which are mainly influenced by airflow limitation related to airway smooth muscle. Mepolizumab improves post-bronchodilator FEV₁ by at least as much as it improves pre-bronchodilator FEV₁, supporting a primary effect on airflow limitation secondary to its effect on airways inflammation. Additionally, there was a positive relationship between baseline blood eosinophil counts and changes in FEV₁ and SGRQ with mepolizumab in MENSA,¹⁰ although this relationship was not as clear as in MUSCA.¹

The tendency for the clinical benefits of mepolizumab to be more obvious in later-stage clinical trials probably reflects the identification of better biomarkers of clinical efficacy, as well as the use of more responsive outcome measures. The results from DREAM⁶ showed that the blood eosinophil count was an independent predictor of the exacerbation reduction with mepolizumab treatment. Moreover, the dose-response relationship for the effect of mepolizumab on exacerbations was dissociated from the effects on sputum eosinophil counts; clinical efficacy related much more closely to the effects of the different doses of mepolizumab on the blood eosinophil counts. The implication of these findings is that the peripheral blood eosinophil count is not only the stand-out biomarker of treatment response, but also the likely treatment target. Criteria based on blood eosinophil counts have been used to identify patients with severe eosinophilic asthma in all mepolizumab studies since DREAM, and a subsequent meta-analysis¹⁰ has confirmed the utility of this biomarker as a predictor of treatment response.

The mepolizumab development story illustrates how important it is to learn lessons from early-phase clinical trials and to adapt outcome measures and patient criteria accordingly. As a result, important clinical efficacy has been noted in a readily identified patient population. The findings of MUSCA also raise two further questions. First, do the benefits of mepolizumab on SGRQ, and the 200–300 mL improvement¹ in post-bronchodilator FEV₁ in patients with a baseline blood eosinophil count greater than 500 cells per μ L justify treatment independent of a predicted beneficial effect on exacerbation frequency? This sort of clinical benefit would be difficult to achieve with any other available treatment so this is a question for regulators and guideline groups to consider very carefully. Second, can the short-term effects of treatment on a responsive

measure such as SGRQ be used to identify patients who are responding to treatment and are therefore likely to have long-term reductions in exacerbation frequency? Identification of an early-response marker is an important priority because biological treatments are likely to be expensive, so health-care payers will be keen for decisions about treatment efficacy to be made early. Such an identification presents challenges however, since interpretation of post-treatment changes are confounded by placebo effects and a strong tendency for regression to the mean. This approach might also not be valid because the mechanism of short-term improvement in SGRQ and long-term reduction in exacerbations differ. It is more likely that treatment decisions will, for the first time in airways disease, be based on measures of the relevant pathological pathway. Longer-term treatment goals could be set, and failure to achieve these should prompt a re-evaluation of the importance of that pathway and a consideration of alternative treatable biomarkers.

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