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Mepolizumab, SGRQ and severe eosinophilic asthma

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It is now ten years since the publication of the first clinical trial, eight years since the first key proof of concept studies in a population selected on the basis of inflammatory pattern[1,2] and two years since approval of Mepolizumab as a treatment for severe eosinophilic asthma. In some countries the treatment has been available to treat patients for over a year. One striking finding of the clinical development programme for this first-in-class anti-IL-5 biological agent has been that evidence for clinical efficacy has become more obvious as we have moved from the first clinical studies[3,4] to phase 2b[5] and then phase 3 trials[6,7] (table). In this issue of the journal Chupp et al[8] report the findings of a phase 3b study, which continues this trend (table).

MUSCA was a placebo-controlled, randomised, double-blind, parallel-group, multicentre study conducted in 146 hospitals/research centres across 19 countries. Patients had severe eosinophilic asthma and a history of ≥2 exacerbations in the previous year despite regular high-dose inhaled corticosteroids plus other controller(s) and were randomised 1:1 to receive mepolizumab 100 mg or placebo subcutaneously every 4 weeks for 24 weeks. Eosinophilic asthma was defined as it was in the phase 3 MENSA trial: a peripheral blood eosinophil count >150 cells/mm^3 at study entry and/or >300 cells/mm^3 in the last year. The primary endpoint was St George's Respiratory Questionnaire (SGRQ) total score at Week 24.

556 patients were randomised (mepolizumab n=276; placebo n=280) and 551 (mepolizumab n=274; placebo n=277) were included in the modified intent-to-treat population. Compared to placebo, patients treated with mepolizumab showed significant improvements from baseline in SGRQ total score, with a mean treatment differences of −7·7, approximately double the previously defined minimally clinically important difference (MCID),[9] and similar to the estimate of the treatment effect on this measure in the phase 3 MENSA trial. The current study extended these earlier findings by showing that important reductions in SGRQ were seen as early as week 4 and that the dominant effect of treatment was on the symptom domain of the SGRQ. Collectively these results suggest that the

SGRQ is a more responsive measure than other more traditional measures of symptoms and quality of life 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 measures is that the symptom domain of the SGRQ better identifies morbidity resulting from inflammation related phenomenon such as mucus plugging, airway wall oedema and structural airway changes than ACQ and AQLQ, which are primarily influenced by airway smooth muscle related airflow limitation. Mepolizumab improves post-bronchodilator at least as much as pre-bronchodilator FEV_1, supporting a primary effect on airflow limitation secondary to airway inflammation. Additional support is provided by the positive relationship between baseline blood eosinophil count and change in both FEV_1 and SGRQ with mepolizumab treatment seen in MENSA[10], although these relationships were not seen as clearly in the MUSCA study.

The tendency for the clinical benefits of mepolizumab to be more obvious in later stage clinical trials likely reflects the identification of better biomarkers of clinical efficacy as well as the use of more responsive outcome measures. DREAM[5] showed that the blood eosinophil count was an independent predictor of the exacerbation reduction seen with mepolizumab treatment. Moreover, there was a dissociation of the dose-response relationship for the effect of mepolizumab on exacerbations from the effects on sputum counts; clinical efficacy related much more closely to the effect of the different doses of mepolizumab on the blood eosinophil count. The clear 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. Blood eosinophil based criteria have been used to identify eosinophilic patients in all studies since DREAM and a subsequent meta-analysis[10] 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 earlier phase clinical trials and adapt outcome measures and patient criteria accordingly. The result of this process has been the identification of important clinical efficacy in a readily identified patient population. The findings of MUSCA raise two further questions. First, are the very large benefits of mepolizumab on SGRQ, and the 200-300 ml improvement[7] in post-bronchodilator FEV_1 seen in patients with a baseline blood eosinophil count > 500 cells/mm^3 sufficiently impressive to justify treatment independent of a predicted beneficial effect on exacerbation frequency? It would be hard to achieve this sort of clinical benefit 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 longer-term reductions in exacerbation frequency? Identification of an early response marker is an important priority as biological treatments are likely to be expensive so health care payers will be keen for treatment efficacy decisions to be made early. This presents challenges as interpretation of post-treatment changes will be confounded by placebo effects and a strong tendency for regression to the mean. It is also possible that this approach is not 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 traits.

References

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Table: Summary of main outcomes of trials of Mepolizumab in asthma

	Population	Dose	Exacerbation reduction (%)	Increase in pre-bronchodilator FEV_1 (ml)	Reduction in ACQ5	Increase in AQLQ	Reduction in SGRQ
Flood Page[4]	Moderate to severe asthma No selection on inflammation or exacerbations	250, 750 mg IV 4 weekly for 12 weeks	-	-40 (-150, 60) to -50 (-160, 60)	-	-	-
Proof of concept[1]	>2 exacerbations/year Sputum eos >3% in last year	750 mg IV 4 weekly for 50 weeks	43 (8, 68)	-50* (-260, 150)	-0.04 (0.38, -0.46)	0.35 (0.08 to 0.63)	-
DREAM[5]	2 or more exacerbations/year One or more of the following in last year: FeNO>50 ppb; sputum eos >3%; blood eos >300 cells/mm^3; prompt deterioration with 25% reduction in corticosteroid dose	75, 250 or 750 mg IV 4 weekly for 52 weeks	39 (19, 54) to 52 (36, 64)	56 (–43, 155) to 81 (–19, 180)	0·16 (-0.07, 0·39) to 0·27 (-0.04, 0·51)	0·05 (–0·19, 0·29) to 0·22 (–0·02, 0·46)	-
MENSA[7]	2 or more exacerbations/year Blood eos > 150 and/or >300 cells/mm^3 in last year	75 mg IV or 100 mg SC 4 weekly for 32 weeks	47 (29, 61) to 53 (37, 65)	98 (11, 184) to 100 (13, 187)	0.42 (0.23, 0.61) to 0.44 (0.25, 0.63)	-	6.4 (3.2, 9.7) to 7.0 (3.8, 10.2)

MUSCA[8]	2 or more exacerbations/year Blood eos > 150 and/or >300 cells/mm^3 in last year	100 mg SC 4 weekly for 24 weeks	58 (44, 69)	120 (47, 192)	0·40 (0.22, 0·58)	-	7·7 (4.9, 10·5)

*Post-bronchodilator; eos=eosinophils; ACQ5 is the five item Asthma Control Questionnaire; AQLO is the Asthma Quality of Life Questionnaire; SGRQ is the Saint George's Respiratory Questionnaire.