

Mepolizumab: A Review in Eosinophilic Asthma

Emma D. Deeks¹

Published online: 16 June 2016
© Springer International Publishing Switzerland 2016

Abstract Mepolizumab (Nucala[®]) is a humanized monoclonal antibody against interleukin-5, a cytokine involved in the development, recruitment and activation of eosinophils (cellular mediators of airway inflammation, hyper-responsiveness and tissue remodelling). The drug is indicated as an add-on treatment for severe eosinophilic asthma, on the basis of its clinical benefit in this setting in the placebo-controlled DREAM, MENSA and SIRIUS trials. Based on the 52-week, phase II, DREAM study (which assessed varying intravenous mepolizumab dosages), intravenous mepolizumab 75 mg every 4 weeks (q4w) and the corresponding (recommended) subcutaneous dosage of 100 mg q4w were studied in the 32- and 24-week phase III MENSA and SIRIUS trials. In patients aged ≥ 12 years with severe eosinophilic asthma in the phase III studies, adding subcutaneous mepolizumab 100 mg q4w to current asthma therapy significantly reduced the rate of clinically relevant asthma exacerbations and, in those dependent on oral glucocorticoids (OCSs) for asthma control, enabled the daily OCS dose to be significantly reduced, relative to adding placebo. This mepolizumab regimen also significantly improved asthma control, health-related quality of life and (in one of the two studies) lung function, and had acceptable tolerability (with

headache the most common adverse event). In the MENSA and SIRIUS extension, COSMOS, mepolizumab provided durable clinical benefit over up to 84 weeks' therapy with no new tolerability concerns. Thus, mepolizumab is a valuable add-on treatment option for adults and adolescents aged ≥ 12 years who have severe eosinophilic asthma despite optimized standard therapies.

Mepolizumab: clinical considerations in severe eosinophilic asthma

Humanized monoclonal antibody to interleukin-5

Reduces blood and sputum eosinophil counts

Reduces asthma exacerbation rates and, in patients dependent on OCSs for asthma control, enables reductions in daily OCS dose

Improves asthma control and health-related quality of life and, in some instances, lung function

Sustains these benefits longer term (≥ 84 weeks' therapy)

Acceptable tolerability profile

The manuscript was reviewed by: *E. Günay*, Department of Chest Diseases, Afyon Kocatepe University School of Medicine, Afyonkarahisar, Turkey; *C. Incorvaia*, Pulmonary Rehabilitation, ASST Gaetano Pini/CTO, Milan, Italy; *I. D. Pavord*, Nuffield Department of Medicine Research, University of Oxford, Oxford, UK.

✉ Emma D. Deeks
demail@springer.com

¹ Springer, Private Bag 65901, Mairangi Bay, 0754 Auckland, New Zealand

1 Introduction

Eosinophilic asthma is one of several distinct asthma subphenotypes, each driven by unique pathophysiological mechanisms [1]. It is characterized by the presence of eosinophils in the lungs, with tissue and sputum eosinophilia [1, 2]. Eosinophils play an integral role in the innate immune responses that occur in the airways (e.g. against

allergens and viral infections), with their activation resulting in the release of various proinflammatory mediators that can lead to airway inflammation [2].

Although airway eosinophil counts can often be reduced by treating patients conventionally with inhaled corticosteroids, some patients (around half of those with severe asthma) have persistent airway eosinophilia, symptoms and exacerbations, regardless of high-dose inhaled corticosteroid use, highlighting the need for additional treatment options in this setting [2]. Consequently, there is growing interest in therapies capable of targeting some of the pivotal pathophysiological elements that may underlie the asthma and allergic responses in such patients.

Interleukin-5 (IL-5) is crucial in promoting the development, recruitment and activation of eosinophils, making it an obvious candidate for targeted asthma therapy [1, 2]. Mepolizumab (Nucala®) is a humanized IgG1/ κ monoclonal antibody against IL-5 [3] that is approved as an add-on treatment for patients with severe eosinophilic asthma in various countries (including the USA [4] and those of the EU [5]) and for a similar indication in Japan [6]. This article focuses on pharmacological, therapeutic efficacy and tolerability data relevant to the use of mepolizumab in this setting and, wherever possible, the recommended regimen of subcutaneous mepolizumab 100 mg every 4 weeks (q4w).

2 Pharmacodynamic Properties of Mepolizumab

Mepolizumab is an antagonist of IL-5 [3], inhibiting the bioactivity of this cytokine by binding to it with high affinity (dissociation constant 100 pmol/L [4]) and specificity, thus preventing it from interacting with IL-5 receptor complexes (each comprising an α and β subunit) on the surface of eosinophils [3, 4]. The concentration of mepolizumab required to inhibit the binding of IL-5 to its receptor by 50 % in vitro was 0.94 nmol/L [3]. Through inhibition of IL-5 signalling, mepolizumab reduces eosinophil production and survival, although the exact mechanism of action underlying the drug's benefit in patients with severe eosinophilic asthma (Sect. 4) has not yet been definitively established [4].

Reductions in blood and/or sputum eosinophil counts were observed with various subcutaneous or intravenous mepolizumab regimens in patients with asthma in randomized trials [7–16]. For instance, in a 12-week open-label study in which 70 adults with asthma and >300 blood eosinophils/ μL (or $\geq 200/\mu\text{L}$ after protocol amendment) received subcutaneous mepolizumab 12.5, 125 or 250 mg or intravenous mepolizumab 75 mg q4w, there was a dose-dependent reduction in both blood and sputum eosinophil count [7]. Of note, blood eosinophil levels were markedly

reduced with each of the mepolizumab regimens by the first post-dose measurement (i.e. day 3), and it was estimated that treatment with subcutaneous mepolizumab at dosages of 11 or 99 mg q4w would be associated with 50 and 90 % maximal inhibition of blood eosinophils, respectively [7].

In phase III trials, known as MENSA [14] and SIRIUS [15], in patients with severe eosinophilic asthma (Sect. 4), reductions in blood eosinophil counts were seen at the first blood draw (i.e. after 4 weeks of treatment) with the recommended mepolizumab regimen (i.e. 100 mg administered subcutaneously q4w) and were subsequently maintained for the remainder of these 24- [15] or 32- [14] week studies, with similar findings reported with the corresponding intravenous mepolizumab dosage (Sect. 3) of 75 mg q4w [14]. This intravenous mepolizumab dosage was near the top of the dose-response curve in terms of reducing blood eosinophil counts over 52 weeks in an earlier dose-ranging phase II study in a similar asthma population (DREAM; Sect. 4) [16]. Longer term, reductions in blood eosinophil counts in patients who had received mepolizumab in MENSA or SIRIUS were subsequently maintained with continued mepolizumab therapy in the 52-week extension of these trials (see Sect. 4) [17].

Patients with eosinophilic asthma who stop taking mepolizumab may experience increases in asthma exacerbation rates, according to 12 months' observation [18] following a 12-month study [12]. However, the increase in symptoms was not considered to be a rebound phenomenon, as no worsening of eosinophilic airway inflammation or changes in other clinical parameters occurred during the observation period.

Antibodies against mepolizumab may develop in some recipients. For instance, in placebo-controlled trials, anti-mepolizumab antibodies were detected in 6 % of 260 subjects who received at least one dose of subcutaneous mepolizumab 100 mg [4, 5]. Although the clinical relevance of these antibodies is not yet known [4], they were neutralizing in only one subject, generally did not alter the drug's pharmacological profile, and did not appear to correlate with changes in blood eosinophil count [4, 5].

3 Pharmacokinetic Properties of Mepolizumab

The pharmacokinetics of subcutaneous mepolizumab are approximately dose proportional across doses of 12.5–250 mg in patients with asthma [4, 5]. Absorption of mepolizumab is slow following administration via this route, reaching maximal plasma concentrations in a median time of 4–8 days in patients with asthma or healthy volunteers [5, 7]. When administered in the arm of patients with asthma, subcutaneous mepolizumab had an absolute

bioavailability of 74–80 % [4, 5, 7]; corresponding values after subcutaneous administration of a single mepolizumab dose in the arm, abdomen or thigh of healthy volunteers were 75, 64 and 71 %, respectively [5]. Of note, a 100 mg subcutaneous dose of mepolizumab is considered to equate to a 75 mg intravenous dose of the drug, based on the absolute bioavailability of the subcutaneous administration route [7]. At steady state, there is approximately twofold accumulation of mepolizumab, when administered subcutaneously q4w [4, 5, 7].

In patients with asthma, mepolizumab has an estimated central volume of distribution of 3.6 L in those weighing 70 kg [4]. Metabolism of mepolizumab occurs via widely distributed proteolytic enzymes [4, 5]. The drug has a mean terminal elimination half-life ($t_{1/2}$) of 16–22 days after subcutaneous administration [4, 5], and an estimated apparent systemic clearance of 0.28 L/day for a patient with asthma weighing 70 kg [4].

Pharmacokinetic data for mepolizumab in the paediatric setting are currently limited. In the few adolescents with severe eosinophilic asthma participating in phase III trials, the pharmacokinetic profile of the drug was generally consistent with that seen in adults [5], although the mean apparent clearance was 35 % lower (vs. adults) in the nine adolescents who received subcutaneous mepolizumab 100 mg q4w [4]. According to a population pharmacokinetic analysis, mepolizumab pharmacokinetics (including clearance [4]) are not affected by age (12–82 years) [4, 5]. Consequently, no dosage adjustments are required in the elderly [4, 5], although in the USA [4], cautious dose selection is recommended in elderly patients, due to the increased likelihood of concomitant diseases/therapies and impaired renal, hepatic and/or cardiovascular function.

Mepolizumab pharmacokinetics are not expected to be affected by renal impairment [based on population pharmacokinetic analyses and the drug's lack of renal clearance, although data in patients with creatinine clearance (CR_{CL}) <50 mL/min are limited] or by hepatic impairment (as metabolism of the drug is not restricted to the liver); where specified, the mepolizumab dosage does not require adjustment in patients with renal (CR_{CL} 50–80 mL/min) or hepatic impairment [4, 5]. Gender and race have no significant effect on mepolizumab clearance, according to population pharmacokinetic analysis [4]. Indeed, the pharmacokinetic profile of the drug appears to be similar between individuals of Japanese and Western origin [19]. For instance, across single intravenous doses of 10–750 mg in healthy Japanese subjects, mepolizumab displayed dose-proportional pharmacokinetics and a mean $t_{1/2}$ of 19.8–36.1 days [19].

The drug interaction potential of mepolizumab has not been formally assessed, although it appears to be low [4, 5]. For instance, mepolizumab exposure was not affected by

the small-molecule drugs often coadministered in phase III trials, according to population pharmacokinetic analyses [4], and mepolizumab clearance does not involve protein-binding mechanisms, CYP enzymes or efflux pumps [5]. Pro-inflammatory cytokines may, if present at increased levels, suppress CYP enzyme and drug transporter formation, through interaction with hepatocyte-expressed cognate receptors; however, the α subunit of the IL-5 receptor does not appear to be expressed on hepatocytes, and systemic proinflammatory markers are only minimally elevated in severe asthma [5].

4 Therapeutic Efficacy of Mepolizumab

As mepolizumab targets eosinophilic inflammation, and given its lack of clinical benefit in early trials in patients with mild or moderate asthma (as per clinical/ physiological criteria) [9, 10], it was hypothesized that patients with persistent eosinophilic asthma may benefit more from the drug, with two small ($n \leq 61$) studies later confirming this [12, 13]. This section focuses on three randomized, double-blind, placebo-controlled trials that evaluated the efficacy of adding mepolizumab to background therapy in patients aged ≥ 12 years with severe refractory eosinophilic asthma [14–16]. These studies were of 24–52 weeks' duration and were primarily designed to assess either asthma exacerbations (DREAM [16] and MENSA [14]) or oral corticosteroid (OCS)-sparing effects (SIRIUS [15]). Data from a 52-week, open-label, phase IIIb extension study of MENSA and SIRIUS (COSMOS) are also discussed [17, 20].

The exacerbation trials [14, 16] enrolled patients who had experienced two or more severe asthma exacerbations in the last year despite receiving high-dose inhaled corticosteroids (with or without OCS therapy) plus other controller medications. In the OCS-sparing trial [15], patients were required to have received systemic corticosteroids as maintenance therapy for ≥ 6 months in addition to high-dose inhaled corticosteroids plus another controller; exacerbations in the last year were not necessary.

Lung function criteria also needed to be met in the exacerbation studies [14, 16], of which the key in MENSA was a forced expiratory volume in 1 s (FEV_1) of <80 % of predicted (in adults) or an FEV_1 <90 % of predicted and/or an FEV_1 :forced volume capacity ratio of <0.8 (in adolescents aged <18 years) [14]. Others included ≥ 20 % FEV_1 variability between two clinic visits in the last year [14, 16] and FEV_1 reversibility of >12 % [14, 16] and 200 mL [16].

Various eosinophilic inclusion criteria were used in the phase II DREAM trial [16] and, on the basis of this study, two were selected for the phase III MENSA and SIRIUS trials: a blood eosinophil count of ≥ 300 cells/ μ L in the last

year [14, 15] or ≥ 150 cells/ μ L at screening [14] or during the optimization phase [15]. The optimization phase was the first of four phases of SIRIUS; it was a pre-randomization period of 3–8 weeks during which the lowest maintenance dose of OCS with acceptable asthma control was established [15]. Subsequent phases included an induction phase (weeks 0–4) in which patients (now randomized to study drug) received optimized OCS therapy; a reduction phase (weeks 4–20) in which the optimal OCS dosage was reduced q4w according to asthma control and adrenal insufficiency; and a maintenance phase (weeks 20–24) during which the OCS dosage was not altered. Patients received mepolizumab or placebo at 4-weekly intervals through weeks 0–20 of this study [15].

Across the three trials, patients had an asthma duration of 19–20 years, a pre-bronchodilator FEV₁ of 1.8–1.95 L, and had experienced a mean of 3.1–3.6 severe asthma exacerbations per year; 17–24 % of patients had been hospitalized in the last year for exacerbations [14–16]. Almost half (48.1 %) of the SIRIUS participants had received OCSs for ≥ 5 years [15], and some patients in DREAM (30.5 %) [16] and MENSA (25.0 %) [14] were also using oral corticosteroids as part of their maintenance therapy. The mean patient age across the three studies was ≈ 50 years [14–16]; the phase III trials included a total of 28 patients aged 12–17 years, 25 of whom were enrolled in SIRIUS [4].

Mepolizumab was administered subcutaneously [14, 15] and/or intravenously [14, 16] q4w at varying doses in these three trials (Table 1). As the intravenous mepolizumab dosages studied in DREAM (75, 250 and 750 mg q4w) provided similar clinical benefit (Table 1) [16], the lowest intravenous dosage of 75 mg q4w, and corresponding subcutaneous dosage of 100 mg q4w (which is expected to provide similar exposure; Sect. 3), were selected for study in MENSA and SIRIUS [21]. Patients in COSMOS ($n = 651$) also received this recommended subcutaneous mepolizumab dosage [17]. Discussion here focuses on subcutaneous mepolizumab 100 mg q4w, wherever possible; key data for intravenous dosages are tabulated for completeness. Some data are sourced from abstracts/posters [17, 20, 22, 23].

4.1 Exacerbations

The addition of mepolizumab to background asthma therapy was effective in reducing the rate of clinically significant asthma exacerbations in patients aged ≥ 12 years with severe eosinophilic asthma [14–16], including those dependent on OCSs for asthma control [15] (Table 1). Compared with placebo over 32 weeks in MENSA, subcutaneous mepolizumab 100 mg q4w significantly reduced the yearly rate of such exacerbations per patient by 53 %

(primary endpoint), and the rate of exacerbations requiring hospitalization or hospitalization/emergency department (ED) visits by 69 and 61 %, respectively (Table 1) [14]. Similarly, in SIRIUS, the yearly rate of clinically significant exacerbations per patient was significantly reduced by 32 % over 24 weeks' treatment with subcutaneous mepolizumab 100 mg q4w (Table 1) [15].

The exacerbation-lowering benefits of mepolizumab in MENSA and SIRIUS were maintained with continued use of the drug for a further 52 weeks in COSMOS (i.e. total of up to 84 weeks' therapy), according to post hoc analyses ($n = 311$ from MENSA; $n = 57$ from SIRIUS) [17, 20]. For instance, among the COSMOS participants who had received mepolizumab in MENSA, 0.92 exacerbations occurred per patient per year, both during weeks 0–20 and 20–52 of COSMOS [17]. Patients from either trial who switched from placebo to mepolizumab at the start of COSMOS ($n = 159$ from MENSA; $n = 58$ from SIRIUS) had improvements in exacerbation rate over 52 weeks that were consistent with those seen with the drug in MENSA and SIRIUS [17, 20].

4.2 Corticosteroid Use

Glucocorticoid-sparing benefits were demonstrated with subcutaneous mepolizumab 100 mg q4w [14, 15]. For instance, during weeks 20–24 of SIRIUS, patients with OCS dependence who had received subcutaneous mepolizumab were significantly more likely than those who had received placebo to have a reduced daily OCS dose compared with the optimization phase (primary outcome), as per the five categories presented in Fig. 1 [15]. The median daily OCS dose during the optimization phase was 10.0 and 12.5 mg in the respective groups.

Mepolizumab also provided significant ($p < 0.05$) benefit relative to placebo for most secondary measures of OCS-sparing in SIRIUS, including the median reduction from baseline in OCS dose at 24 weeks (50 vs. 0 %) and the proportion of patients whose daily OCS dose was reduced by ≥ 50 % (54 vs. 33 %) or to ≤ 5 mg (54 vs. 32 %); however, the proportion of mepolizumab or placebo recipients who completely stopped OCSs did not significantly differ (14 vs. 8 %) [15].

Similarly, in MENSA, subcutaneous mepolizumab recipients used 43 % less systemic glucocorticoids than placebo recipients for the treatment of exacerbations (45 vs. 79 g), and the duration of such glucocorticoid use was almost twofold shorter in the mepolizumab group (1096 vs. 2037 days with placebo) [14].

The OCS-sparing benefits of mepolizumab seen in the 24-week SIRIUS trial were maintained with continued use of the drug for a further 52 weeks in COSMOS, with the median OCS dosage being ≈ 2.5 mg/day, both at the start

Table 1 Efficacy of mepolizumab in reducing asthma exacerbations when added to background therapy in patients aged ≥ 12 years with severe eosinophilic asthma

Trial (duration; weeks)	Treatment [mg q4w; admin route] (pt no)	Number of exacerbations per pt per year (rate ratio ^a vs. PL; 95 % CI)		
		Clinically significant ^b	Requiring hospitalization/ED visit ^c	Requiring hospitalization ^c
DREAM (52) [16]	MEP 75 IV (153)	1.24 (0.52; 0.39–0.69)***	0.17 (0.40; 0.19–0.81)	0.11 (0.61; 0.28–1.33)
	MEP 250 IV (152)	1.46 (0.61; 0.46–0.81)**	0.25 (0.58; 0.30–1.12)	0.12 (0.65; 0.31–1.39)
	MEP 750 IV (156)	1.15 (0.48; 0.36–0.64)***	0.22 (0.52; 0.27–1.02)	0.07 (0.37; 0.16–0.88)
	PL (155)	2.40	0.43	0.18
MENSA (32) [14]	MEP 100 SC (194)	0.83 (0.47; 0.35–0.64)**	0.08 (0.39; 0.18–0.83)*	0.03 (0.31; 0.11–0.91)*
	MEP 75 IV (191)	0.93 (0.53; 0.40–0.72)**	0.14 (0.68; 0.33–1.41)	0.06 (0.61; 0.23–1.66)
	PL (191)	1.74	0.20	0.10
SIRIUS (24) [15]	MEP 100 SC (69)	1.44 (0.68; 0.47–0.99)*		
	PL (66)	2.12		

Results from phase II or III trials. MEP is not indicated for IV use

Admin administration, ED emergency department, IV intravenous, MEP mepolizumab, PL placebo, pt patient, q4w every 4 weeks, SC subcutaneous

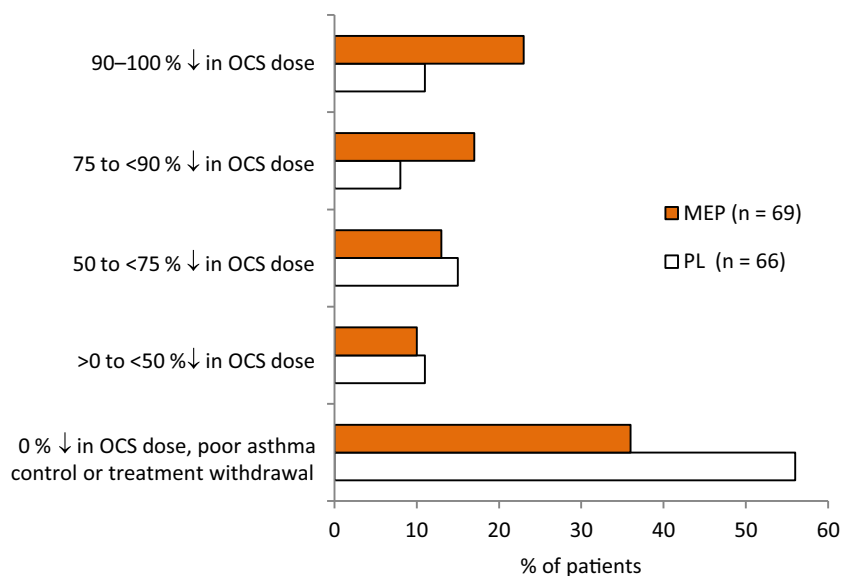
* $p < 0.05$, ** $p < 0.001$, *** $p < 0.0001$ vs. PL

^a Rate ratios reported for MENSA were converted from percentage differences vs. PL

^b Primary endpoint of DREAM and MENSA

^c P values vs. PL were not reported for this parameter in the DREAM study

Fig. 1 Categories of the primary efficacy outcome ‘percentage reduction in daily oral glucocorticoid dose during the maintenance (i.e. weeks 20–24) vs. optimization phase’ in patients with severe eosinophilic asthma in SIRIUS [15]. Odds ratio across all categories for mepolizumab vs. placebo was 2.39 (95 % CI 1.25–4.56; $p = 0.008$). *MEP* subcutaneous mepolizumab 100 mg every 4 weeks, *OCS* oral glucocorticoid, *PL* placebo



and end of the extension [20]. Patients who switched from placebo to mepolizumab at the start of COSMOS experienced OCS-sparing effects over 52 weeks, consistent with those seen with the drug in SIRIUS [20].

4.3 Lung Function, Asthma Control and Health-Related Quality of Life

Subcutaneous mepolizumab 100 mg q4w improved lung function in both MENSA [14] and SIRIUS [15], although statistical significance relative to placebo (where reported) was reached only in MENSA (the larger of these two studies). At week 32 in MENSA, subcutaneous mepolizumab was associated with significant ($p < 0.05$) increases relative to placebo in FEV_1 , both before and after bronchodilation (respective between-group differences were 98 and 138 mL), with the mepolizumab group also experiencing a 16-fold improvement from baseline in peak expiratory flow (PEF) versus the placebo group (29.5 vs. 1.8 L/min; statistical analysis not reported) [14]. At week 24 in SIRIUS, pre- and post-bronchodilator FEV_1 had not changed from baseline to a significantly greater extent in mepolizumab versus placebo recipients (between-group differences were 114 and 128 mL) [15].

Control of asthma symptoms was improved with subcutaneous mepolizumab in these studies, as measured by the 5-item Asthma Control Questionnaire (ACQ-5) [0–6 score range, with higher scores indicating worse control, and 0.5 being the minimal clinically important difference]. Relative to placebo recipients, mepolizumab recipients had significant ($p \leq 0.004$) improvements (i.e. reductions) in mean ACQ-5 score at week 32 in MENSA (between-group difference -0.44) [14] and at week 24 in SIRIUS

(between-group difference -0.52) [15], with marked numerical improvements evident with mepolizumab versus placebo from week 4 [14] and 2 [15] in the respective trials.

Subcutaneous mepolizumab also improved health-related quality of life (HR-QOL), as assessed using the St. George's Respiratory Questionnaire (SGRQ) [0–100 score range, with higher scores indicating worse HR-QOL, and a score change of 4 being clinically relevant]. The SGRQ score was significantly ($p \leq 0.02$) reduced (i.e. improved) in mepolizumab versus placebo recipients at 32 weeks in MENSA (between-group difference of -7.0) [14] and 24 weeks in SIRIUS (between-group difference of -5.8) [15].

Longer term, among the mepolizumab recipients of MENSA and SIRIUS who entered COSMOS, lung function, asthma control and HR-QOL were generally maintained over a further 52 weeks of mepolizumab therapy [17].

4.4 Pooled and Subgroup Analyses

The efficacy of mepolizumab in reducing asthma exacerbation rates in patients with severe eosinophilic asthma is supported by a meta-analysis of data from placebo-controlled trials [22]. For instance, when DREAM and MENSA data were combined for subcutaneous mepolizumab 100 mg q4w and intravenous mepolizumab 75 mg q4w ($n = 538$) and compared with corresponding combined placebo data ($n = 346$), mepolizumab significantly ($p \leq 0.027$) reduced the overall rate of exacerbations requiring hospitalization by 48 % and those requiring ED visits/hospitalization by 54 % (coprimary endpoints of the meta-analysis) [22].

Another combined analysis (post hoc; $n = 1185$) of these two trials (including all mepolizumab dosages) indicated that the drug significantly reduced the yearly rate of clinically significant exacerbations versus placebo, regardless of baseline blood eosinophil count, although the magnitude of the reduction progressively increased with increasing eosinophil count (e.g. 52 % at ≥ 150 cells/ μL to 70 % at ≥ 500 cells/ μL) [24]. Individual analyses of DREAM (all intravenous mepolizumab dosages, pooled) [16, 24] and MENSA (subcutaneous and intravenous dosages pooled) [14, 24] reported similar findings. In the 177 patients whose baseline eosinophil count was high (≥ 500 cells/ μL) in MENSA, subcutaneous mepolizumab 100 mg q4w, compared with placebo, considerably improved the clinically significant exacerbation rate by 80 %, pre- and post-bronchodilator FEV₁ by 132 and 222 mL, SGRQ score by 8.9 points and ACQ score by 0.75 points [14].

Having ≥ 150 blood eosinophils/ μL at baseline appeared to be predictive of responding to mepolizumab in DREAM [25] and MENSA [4], whereas baseline sputum eosinophil count was not [25]. Notably, among mepolizumab recipients with <150 blood eosinophils/ μL at baseline despite a historical count of ≥ 300 blood eosinophils/ μL , exacerbation rates were reduced by 20 % in DREAM [24] and very little in MENSA [4].

When MENSA data for subcutaneous mepolizumab 100 mg q4w and intravenous mepolizumab 75 mg q4w were pooled and assessed post hoc by age [23], mepolizumab significantly reduced the asthma exacerbation rate relative to placebo by 45 and 76 % in patients aged <65 ($n = 496$) or ≥ 65 ($n = 80$) years. Moreover, among the patients aged 12–17 years in SIRIUS, clinically significant exacerbations occurred in none of the seven treated with subcutaneous mepolizumab 100 mg q4w versus three of the nine who received placebo [5].

Efficacy outcomes for MENSA and SIRIUS have also been assessed post hoc on the basis of patients' treatment history with omalizumab (an IgE-targeted agent for severe allergic asthma; Sect. 7) [26]. In MENSA, mepolizumab (subcutaneous 100 mg q4w or intravenous 75 mg q4w; pooled) significantly (vs. placebo) reduced the clinically significant exacerbation rate (primary outcome), regardless of whether patients had ($n = 75$) or had not ($n = 501$) received omalizumab previously. Each subgroup also had significant improvements (vs. placebo) in HR-QOL and asthma control with mepolizumab, although lung function measures improved significantly (vs. placebo) only in the no prior omalizumab group [26].

Among OCS-dependent patients in SIRIUS, recipients of subcutaneous mepolizumab 100 mg q4w were more than twofold more likely than placebo recipients to have a reduction in daily OCS dose (primary outcome), regardless of having prior ($n = 45$) or no prior ($n = 90$) omalizumab

therapy, although the between-treatment difference reached significance only in the latter (larger) subgroup [26]. With regard to other efficacy measures, mepolizumab provided significant benefit (vs. placebo) for post-bronchodilator FEV₁ in the prior omalizumab group and asthma control and HR-QOL in the no prior omalizumab group [26].

5 Tolerability of Mepolizumab

Mepolizumab, administered subcutaneously or intravenously q4w in addition to background asthma therapy, for up to 84 weeks had an acceptable tolerability profile in patients aged ≥ 12 years with severe eosinophilic asthma (including those dependent on OCSs) in the trials discussed in Sect. 4. Of note, the tolerability profile of mepolizumab in paediatric patients cannot be fully characterized at present due to the paucity of data, although is expected to be consistent with that in adults, in terms of adverse event (AE) type, frequency and severity [5]. This section focuses on subcutaneous mepolizumab 100 mg q4w (i.e. the recommended dosage) unless otherwise specified.

Numerically more mepolizumab than placebo recipients had AEs considered to be related to study drug in the 32-week MENSA (20 vs. 16 %) [14] and 24-week SIRIUS (30 vs. 18 %) [15] trials, although treatment discontinuation and/or study withdrawal because of AEs was uncommon in these studies, regardless of treatment group (1 vs. 2 % [14]; 4 vs. 5 % [15]). The most common AEs with mepolizumab in MENSA and SIRIUS were nonasthma events [14, 15]. Indeed, in a pooled analysis of these trials, the adverse reactions that occurred most frequently

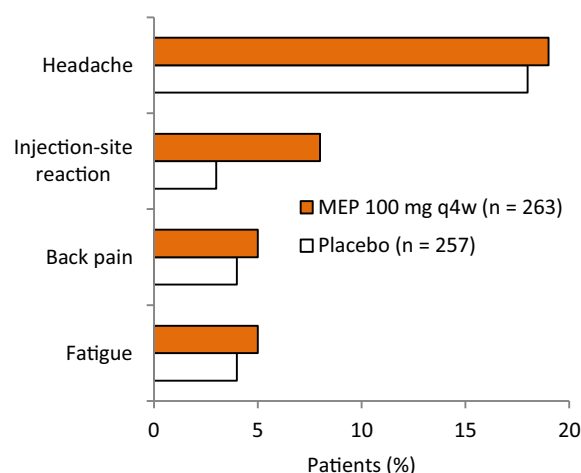


Fig. 2 Most common adverse reactions (incidence ≥ 3 %) that occurred in numerically more subcutaneous mepolizumab 100 mg every 4 weeks than placebo recipients with severe eosinophilic asthma in a pooled analysis of MENSA and SIRIUS [4]. MEP mepolizumab, q4w every 4 weeks

(incidence $\geq 3\%$) and with a numerically greater incidence with mepolizumab than with placebo included headache, injection-site reactions, back pain and fatigue (Fig. 2) [4]. Injection-site reactions were most common at the beginning of treatment (within the first three injections) and were reported less frequently with continued mepolizumab therapy; they were mild or moderate in intensity and usually resolved in a few days [5].

Serious AEs occurred in numerically fewer mepolizumab than placebo recipients during treatment in MENSA (8 vs. 14 %) [14] and SIRIUS (1 vs. 18 %) [15], and were rarely considered to be related to study drug where specified (1 vs. 1 % of patients) [14]. No mepolizumab recipients died in these trials [14, 15].

There have been reports of systemic reactions (including hypersensitivity reactions, such as bronchospasm, angioedema, rash, urticaria and hypotension) with mepolizumab [4, 5]. For instance, in an analysis of DREAM, MENSA and SIRIUS, 10 % of mepolizumab (intravenous or subcutaneous) recipients versus 7 % of placebo recipients had systemic reactions (e.g. rash, myalgia) [4]. These are usually acute, occurring within a few hours of the drug being administered, but can also be delayed, occurring after several days [5]. If a hypersensitivity reaction occurs, mepolizumab discontinuation is recommended in the USA [4].

Herpes zoster virus infections have occurred with mepolizumab therapy [4]. For example, herpes zoster was the only serious AE to occur in more than one patient and with a numerically greater incidence with mepolizumab than with placebo (two vs. no patients) in a pooled analysis of MENSA and SIRIUS [4]. Before starting mepolizumab, varicella vaccination should be considered [4]. In addition, as immunological responses to some helminth infections may involve eosinophils, such infections should be treated before initiating mepolizumab; if helminth infections occur during mepolizumab therapy and are unresponsive to treatment, mepolizumab should be discontinued temporarily [4, 5].

The tolerability profile of mepolizumab (subcutaneous or intravenous) is generally similar in the longer term, according to data from the 52-week extension of MENSA and SIRIUS (COSMOS [17]) and other ongoing open-label extension studies ($n = 998$; no further details reported) [4]. In COSMOS [17], the incidence of cardiovascular AEs was low ($<1\%$) and there were no cases of anaphylaxis related to mepolizumab and no fatal AEs over up to 84 weeks of mepolizumab therapy.

6 Dosage and Administration of Mepolizumab

Mepolizumab is approved in the USA as an add-on maintenance treatment for patients aged ≥ 12 years with severe eosinophilic asthma [4], in the EU as an add-on

treatment for severe refractory eosinophilic asthma in adults [5], and in Japan for patients aged ≥ 12 years with bronchial asthma refractory to standard therapy [6]. The recommended dosage is 100 mg q4w, administered via subcutaneous injection [4–6] into the upper arm, abdomen or thigh [4, 5]. After initiating mepolizumab treatment, corticosteroids should not be discontinued abruptly; if appropriate, corticosteroid doses may be reduced gradually [4, 5]. Mepolizumab should not be used to treat other eosinophilic conditions [4], acute asthma symptoms [4] or exacerbations [4, 5], acute bronchospasm [4] or status asthmaticus [4]. Local prescribing information should be consulted for detailed information regarding preparation and administration instructions, use in special populations, contraindications and other warnings and precautions.

7 Place of Mepolizumab in the Management of Asthma

Asthma is treated in a stepwise manner, with therapy commencing with the pharmacological options most suitable for the severity of disease and then modified as needed to improve/maintain control [27]. Inhaled combination regimens comprising a bronchodilator and a corticosteroid are mainstay asthma treatments [27, 28] that enable $\approx 68\%$ of patients to achieve control of their symptoms [29]. For patients with more severe and uncontrolled asthma, other controller medications are added, such as leukotriene receptor antagonists, theophylline and, at the highest treatment step, oral corticosteroids [27, 28]. However, as not all patients respond adequately to these existing therapies, this ‘one size fits all’ approach is now being challenged by the concept of personalized asthma therapy, taking into account the specific asthma type [29].

For some asthma phenotypes, treatment regimens are now able to include biological agents that target certain asthmatic inflammatory processes [29]. The first of these agents to be introduced was omalizumab, a humanized monoclonal antibody against IgE, which acts by reducing levels of free IgE capable of initiating allergic cascades [30, 31]. Omalizumab is an injectable add-on therapy for patients with severe [30] (or moderate to severe [31]) persistent allergic asthma despite standard treatments, and is recommended as an option in this setting by the most recent Global Initiative For Asthma (GINA) guidelines [27]. More recently, the first targeted treatment option specifically for patients with severe uncontrolled eosinophilic asthma was also made available with the introduction of mepolizumab, a humanized monoclonal antibody against IL-5 (Sect. 2), the key cytokine involved in eosinophil development, recruitment and activation [2].

Mepolizumab is indicated as an add-on treatment for patients with severe eosinophilic asthma (in the USA, EU and some other countries) or with refractory bronchial asthma (in Japan) (Sect. 6), on the basis of its clinical benefit relative to placebo in this setting in phase II (DREAM) and III (MENSA; SIRIUS) trials of 24–52 weeks' duration (Sect. 4). In patients aged ≥ 12 years with severe eosinophilic asthma in the phase III studies, adding subcutaneous mepolizumab 100 mg q4w to current therapy significantly reduced the rate of asthma exacerbations (Sect. 4.1) and, in those dependent on OCGs for asthma control, enabled the daily OCS dose to be significantly reduced (Sect. 4.2), a desirable outcome given the tolerability issues of long-term oral corticosteroid therapy (e.g. osteoporosis, cataracts, stomach ulcers and, in children, reduced growth) [32]. The mepolizumab regimen also significantly improved asthma control, HR-QOL and (in one of the two studies) lung function (Sect. 4.3). In addition to the clinical benefit observed with subcutaneous mepolizumab in these trials, the drug was generally well tolerated (Sect. 5), with the importance of these findings reflected in the fact that GINA now recommend the drug as an option in this setting [27].

Given the chronic nature of asthma, the long-term efficacy and tolerability of therapeutic agents is paramount. Recent data from the MENSA and SIRIUS extension, COSMOS, indicate that mepolizumab provides durable clinical benefit over up to 84 weeks of treatment (Sect. 4), with no new tolerability concerns (Sect. 5). Longer-term data are of interest, as are larger trials solely evaluating the recommended mepolizumab regimen and its efficacy in adolescents (aged 12–17 years) and further studies assessing the potential for rebound worsening of eosinophilic inflammation in the airway following cessation of mepolizumab therapy (Sect. 2). Moreover, although mepolizumab and omalizumab are indicated for different asthma phenotypes, some patients may be eligible for treatment with either agent, making direct head-to-head comparisons of interest. Currently, these agents have only been compared indirectly, with outcomes tending to favour mepolizumab but generally not reaching statistical significance [33]; however, cautious interpretation of these data is necessary given the indirect nature of the comparison and the heterogeneity between the trials included.

For targeted asthma therapies, such as mepolizumab, it is important for the most appropriate patients to be selected to ensure maximal effectiveness. Ideally, such selection should involve careful clinical characterization and use of a biomarker that is easily measured, minimally invasive and reproducible [34]. Sputum eosinophil count (although a reliable airway inflammation marker capable of predicting response to corticosteroids and other anti-inflammatories) was not predictive of mepolizumab response in patients with severe eosinophilic asthma (Sect. 4.4). By contrast, blood

eosinophil count (≥ 150 cells/ μ L) appears to be a promising predictor of mepolizumab response in this setting (Sect. 4.4).

Unlike sputum eosinophils, blood eosinophils can be obtained easily [1], although may fluctuate daily due to their short and variable half-life and sensitivity to various factors, including glucocorticoids [35, 36]. However, analysis of placebo data from MENSA and DREAM indicate that a single blood eosinophil count of ≥ 150 cells/ μ L may be sufficient to identify patients with severe asthma whose blood eosinophils are likely to remain at this level, and are thus suitable for mepolizumab therapy [25, 37]. Further data would be beneficial to confirm these findings, particularly as a number of other monoclonal antibodies to IL-5 (reslizumab) or its receptor (benralizumab) are under development [2]. The cost-effectiveness of mepolizumab also remains to be determined.

In conclusion, subcutaneous mepolizumab is a valuable add-on treatment option for adults and adolescents aged ≥ 12 years who have severe eosinophilic asthma despite optimized standard therapies.

Data selection sources: Relevant medical literature (including published and unpublished data) on mepolizumab was identified by searching databases including MEDLINE (from 1946), PubMed (from 1946) and EMBASE (from 1996) [searches last updated 27 May 2016], bibliographies from published literature, clinical trial registries/databases and websites. Additional information was also requested from the company developing the drug.

Search terms: Mepolizumab, Nucala, SB240563, asthma.

Study selection: Studies in patients with asthma who received mepolizumab. When available, large, well designed, comparative trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Acknowledgments During the peer review process, the manufacturer of mepolizumab was also offered an opportunity to review this article. Changes resulting from comments received were made on the basis of scientific and editorial merit.

Compliance with Ethical Standards

Funding The preparation of this review was not supported by any external funding.

Conflict of interest Emma Deeks is a salaried employee of Adis/ Springer, is responsible for the article content and declares no relevant conflicts of interest.

References

1. Walford HH, Doherty TA. Diagnosis and management of eosinophilic asthma: a US perspective. *J Asthma Allergy*. 2014;7:53–65.
2. Patterson MF, Borish L, Kennedy JL. The past, present, and future of monoclonal antibodies to IL-5 and eosinophilic asthma: a review. *J Asthma Allergy*. 2015;8:125–34.

3. Smith DA, Minthorn EA, Beerahee M. Pharmacokinetics and pharmacodynamics of mepolizumab, an anti-interleukin-5 monoclonal antibody. *Clin Pharmacokinet*. 2011;50(4):215–27.
4. GlaxoSmithKline. Nucala (mepolizumab) for injection, for subcutaneous use: US prescribing information. 2015. <http://www.accessdata.fda.gov>. Accessed 12 May 2016.
5. GlaxoSmithKline Trading Services Limited. Nucala 100 mg powder for solution for injection: EU summary of product characteristics. 2016. <http://www.ema.europa.eu/ema>. Accessed 12 May 2016.
6. GlaxoSmithKline. Nucala for s.c. injection: Japanese prescribing information. 2016. https://www.healthsk.jp/content/dam/global/Health/Master/ja_JP/products-basic-info/nucala/nucala.pdf. Accessed 12 May 2016.
7. Poulquien IJ, Kornmann O, Barton SV, et al. Characterization of the relationship between dose and blood eosinophil response following subcutaneous administration of mepolizumab. *Int J Clin Pharmacol Ther*. 2015;53(12):1015–27.
8. Buttner C, Lun A, Spletstoesser T, et al. Monoclonal anti-interleukin-5 treatment suppresses eosinophil but not T-cell functions. *Eur Respir J*. 2003;21(5):799–803.
9. Leckie MJ, ten Brinke A, Khan J, et al. Effects of an interleukin-5 blocking monoclonal antibody on eosinophils, airway hyper-responsiveness, and the late asthmatic response. *Lancet*. 2000;356(9248):2144–8.
10. Flood-Page P, Swenson C, Faiferman I, et al. A study to evaluate safety and efficacy of mepolizumab in patients with moderate persistent asthma. *Am J Respir Crit Care Med*. 2007;176(11):1062–71.
11. Flood-Page PT, Menzies-Gow AN, Kay AB, et al. Eosinophil's role remains uncertain as anti-interleukin-5 only partially depletes numbers in asthmatic airway. *Am J Respir Crit Care Med*. 2003;167(2):199–204.
12. Haldar P, Brightling CE, Hargadon B, et al. Mepolizumab and exacerbations of refractory eosinophilic asthma. *N Engl J Med*. 2009;360(10):973–84.
13. Nair P, Pizzichini MM, Kjarsgaard M, et al. Mepolizumab for prednisone-dependent asthma with sputum eosinophilia. *N Engl J Med*. 2009;360(10):985–93.
14. Ortega HG, Liu MC, Pavord ID, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med*. 2014;371(13):1198–207.
15. Bel EH, Wenzel SE, Thompson PJ, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. *N Engl J Med*. 2014;371(13):1189–97.
16. Pavord ID, Korn S, Howarth P, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet*. 2012;380(9842):651–9.
17. Albers FC, Lugogo N, Gilson MJ, et al. Long-term safety and efficacy of mepolizumab in patients with severe eosinophilic asthma [poster no. 43]. In: AAAAI Annual Meeting; 2016.
18. Haldar P, Brightling CE, Singapuri A, et al. Outcomes after cessation of mepolizumab therapy in severe eosinophilic asthma: a 12-month follow-up analysis. *J Allergy Clin Immunol*. 2014;133(3):921–3.
19. Tsukamoto N, Takahashi N, Itoh H, et al. Pharmacokinetics and pharmacodynamics of mepolizumab, an anti-interleukin 5 monoclonal antibody, in healthy Japanese male subjects. *Clin Pharmacol Drug Dev*. 2015;5(2):102–8.
20. Prazma CM, Bel EH, Barnes NC, et al. Steroid sparing response with mepolizumab: durability of steroid reduction in severe asthma [poster no. 49]. In: AAAAI Annual Meeting; 2016.
21. European Medicines Agency. Assessment report: Nucala (international non-proprietary name: mepolizumab). 2015. <http://www.ema.europa.eu>. Accessed 12 May 2016.
22. Pavord I, Ortega H, Keene O, et al. A meta-analysis of exacerbations requiring hospitalization from studies of mepolizumab in severe eosinophilic asthma [abstract no. P287 plus poster]. *Am J Resp Crit Care Med*. 2015;191:A4260.
23. Ortega H, Mayer B, Yancey S, et al. Response to treatment with mepolizumab in elderly patients [abstract]. *Am J Respir Crit Care Med*. 2015;191(meeting abstract issue).
24. Ortega HG, Yancey SW, Mayer B, et al. Severe eosinophilic asthma treated with mepolizumab stratified by baseline eosinophil thresholds: a secondary analysis of the DREAM and MENSA studies. *Lancet Resp Med*. 2016. doi:10.1016/S2213-2600(16)30031-5.
25. Katz LE, Gleich GJ, Hartley BF, et al. Blood eosinophil count is a useful biomarker to identify patients with severe eosinophilic asthma. *Ann Am Thorac Soc*. 2014;11(4):531–6.
26. Magnan A, Bourdin A, Prazma CM, et al. Treatment response with mepolizumab in severe eosinophilic asthma patients with previous omalizumab treatment. *Allergy*. 2016. doi:10.1111/all.12914.
27. Global Initiative for Asthma. Pocket guide for asthma management and prevention (for adults and children older than 5 years). 2016. <http://ginasthma.org/2016-pocket-guide-for-asthma-management-and-prevention/>. Accessed 12 May 2016.
28. British Thoracic Society and Scottish Intercollegiate Guidelines Network. British guideline on the management of asthma: a national clinical guideline. <https://www.brit-thoracic.org.uk/document-library/clinical-information/asthma/bttsign-asthma-guideline-2014/>. Accessed 12 May 2016.
29. Chung KF. Defining phenotypes in asthma: a step towards personalized medicine. *Drugs*. 2014;74(7):719–28.
30. Novartis Europharm Limited. Xolair for injection: EU summary of product characteristics. 2016. <http://www.ema.europa.eu/ema>. Accessed 12 May 2016.
31. Novartis Pharmaceuticals Corporation. Xolair® (omalizumab) for injection, for subcutaneous use: US prescribing information. 2015. <http://www.fda.gov>. Accessed 12 May 2016.
32. National Health Service. Corticosteroids - side effects. 2015. [http://www.nhs.uk/Conditions/Corticosteroid-\(drugs\)/Pages/Side-effects.aspx](http://www.nhs.uk/Conditions/Corticosteroid-(drugs)/Pages/Side-effects.aspx). Accessed 12 May 2016.
33. Stynes G, Cockle S, Gunsoy N, et al. Comparative effectiveness of mepolizumab and omalizumab in severe asthma: an indirect comparison [poster no. 271]. In: AAAAI Annual Meeting; 2016.
34. Ortega H, Katz L, Gunsoy N, et al. Blood eosinophil counts predict treatment response in patients with severe eosinophilic asthma [abstract]. *J Allergy Clin Immunol*. 2015;136(3):825–6.
35. Szeffler SJ, Wenzel S, Brown R, et al. Asthma outcomes: biomarkers. *J Allergy Clin Immunol*. 2012;129(3 Suppl):S9–23.
36. Spector SL, Tan RA. Is a single blood eosinophil count a reliable marker for “eosinophilic asthma?”. *J Asthma*. 2012;49(8):807–10.
37. Ortega H, Gleich G, Mayer B, et al. Reproducibility of a single blood eosinophil measurement as a biomarker in severe eosinophilic asthma [letter]. *Ann Am Thorac Soc*. 2015;12(12):1896–7.