Mepolizumab versus placebo for asthma

Review information

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What's new

Date	Event	Description

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Date	Event	Description

Abstract

Background

Mepolizumab is a human monoclonal antibody against interleukin-5 (IL-5), the main cytokine involved in the activation of eosinophils, which in turn causes airway inflammation. Recent studies have suggested these agents may have a role in reducing exacerbations and improving health-related quality of life (HRQoL). There are no recommendations for the use of mepolizumab in adults or children in the recent update of the BTS/SIGN guidelines (BTS/SIGN 2014).

Objectives

To compare the effects of mepolizumab with placebo on exacerbations and HRQoL in adults and children with chronic asthma.

Search methods

We searched the Cochrane Airways Group Register (CAGR) of trials, clinical trial registries, manufacturers' websites and the reference lists of included studies. Searches were conducted in November 2013 and updated in November 2014.

Selection criteria

We included randomised controlled trials comparing mepolizumab versus placebo in adults and children with asthma.

Data collection and analysis

Two authors independently extracted data and analysed outcomes using a random-effects model. We used standard methods expected by The Cochrane Collaboration.

Main results

Eight studies on 1707 participants met the inclusion criteria. Only two studies included children (over 12 years of age), but they did not report separate findings for the adolescents. Seven studies involved intravenous mepolizumab alone; one included a subcutaneous arm. There was heterogeneity in the severity and clinical pattern of asthma among the participants in the eight studies, varying from mild to moderate atopic asthma, to persistent asthma and eosinophilic asthma with recurrent exacerbations. Selection bias was a concern in several of the studies included in this review.

Four trials compared intravenous mepolizumab to placebo in relation to HRQoL. Two studies measured scores from the Asthma Quality of Life Questionnaire (AQLQ), which showed a non-significant difference between mepolizumab and placebo (mean difference (MD) 0.21, 95% confidence interval (CI) − 0.01 to 0.44; participants = 682), in the direction favouring mepolizumab. The third study used the St. George's Respiratory Questionnaire (SGRQ) and found a significant difference between mepolizumab and placebo (MD 6.40, 95% CI 3.15 to 9.65; participants = 576), which indicated a clinically important benefit favouring mepolizumab. A fourth study noted that there was no significant difference but did not provide any data. The two studies in people with eosinophilic asthma showed a reduction in clinically significant exacerbation rates (Risk Ratio 0.52, 95% CI 0.43 to 0.64; participants = 690). However, an analysis of four studies that were not confined to people with eosinophilic asthma indicated considerable heterogeneity and no significant difference in people with one or more exacerbations between mepolizumab and placebo using a random-effects model (Risk Ratio 0.67, 95% CI 0.34 to 1.31; participants = 468; I^2 = 59%).The analysis of serious adverse events indicated a significant difference favouring mepolizumab (Risk ratio 0.49, 95% CI 0.30 to 0.80; participants = 1441; studies = 5; I^2 = 0%). It was not possible to combine the results for adverse events, and we deemed the quality of this evidence to be low.

A single study compared subcutaneous mepolizumab to placebo in 385 adults with severe eosinophilic asthma and found an improvement in HRQoL scores and a reduction in asthma exacerbations, including exacerbations requiring admission to hospital.

Authors' conclusions

It is not possible to draw firm conclusions from this review with respect to the role of mepolizumab in patients with asthma. Our confidence in the results of this review are limited by the fact that the intravenous route is not currently licensed for mepolizumab, and the evidence for the currently licenced subcutaneous route is limited to a single study in participants with severe eosinophilic asthma.

The currently available studies provide evidence that mepolizumab can lead to an improvement in health-related quality of life scores and reduce asthma exacerbations in people with severe eosinophilic asthma.

Further research is needed to clarify which subgroups of patients with asthma could potentially benefit from this treatment. Dosage, ideal dosing regimens and duration of treatment need to be clarified, as the studies included in this review differed in their protocols. There are no studies reporting results from children, so we cannot comment on treatment for this age group. At the present time, larger studies using licenced treatment regimens are required to establish the role of mepolizumab in the treatment of severe asthma.

Plain language summary

Mepolizumab as opposed to placebo for asthma

Review question

We considered in this review whether taking mepolizumab is better than a placebo for people with asthma.

Background

Asthma is an inflammatory lung condition characterised by the narrowing of the airways, breathlessness, a tight chest and reduced quality of life. By the year 2025, there may be up to 400 million people with asthma worldwide. Mepolizumab is one treatment that may help to reduce the symptoms.

Study characteristics

Eight studies compared mepolizumab treatment to a placebo in 1707 patients with asthma. Six studies only included adults. We summarised the results as they relate to quality of life, occurrence of asthma attacks needing hospital admission and side effects of mepolizumab.

Key results

We found that patients with severe asthma who had high levels of eosinophils (inflammatory cells in the blood stream) benefited from taking mepolizumab through improved quality of life and reduced asthma attacks. There was no benefit in terms of lung function. We have avoided making recommendations because we think that further research is needed to clarify aspects such as dosage and length of treatment as well as which patients might benefit the most.

Background

Description of the condition

A recent global estimate of the number of people currently suffering from asthma is in the region of 300 million, and it is

expected that by 2025 the number will increase to 400 million (WHO 2007). The subsequent burden of disease is likely to continue to impose additional pressures on patients, their families and healthcare systems (Masoli 2004). The increased incidence in morbidity has been associated with suboptimal delivery of care, including under-treatment with corticosteroids and a limited awareness of the condition amongst patients (Gibson 1993; Kandane-Rathayake 2009).

In the USA, the number of people with asthma increased from 20 million in 2001 to 25 million in 2009 (CDC 2011). Prevalence rates are slightly higher among children (10%) than among adults (8%) (CDC 2011; CDC 2012), with considerable variation among different ethnic groups. Between 2008 and 2010, asthma prevalence rates in the USA were 14.1% among multiracial individuals, 11.2% among blacks, 9.4% among Alaska Natives, 9.4% among other Native Americans, 7.7% among whites and 5.2% among those of Asian descent (CDC 2011). Globally, the prevalence of wheezing symptoms in children varies geographically, with the UK having the highest recorded prevalence of current wheezing at 32.3% and Ethiopia the lowest at 1.7% (Patel 2008).

For many people, asthma has an important impact on quality of life (Clayton 2005) and on financial considerations (Wu 2007). In the USA, approximately 10 million people experience asthma exacerbations each year (Krishnan 2006), and in the UK, over 65,000 hospital admissions for asthma were recorded in 2005 and 2006 (NHS 2011).

In recent years, clinical guidelines have been produced for the management of asthma at national (e.g. BTS/SIGN 2014; NIH 2007) and international (GINA 2012) levels. Several risk factors for asthma have been identified, including triggers such as allergens, chemical irritants and tobacco smoke, but asthma-related mortality and morbidity remain a major health concern (Braman 2006). On the other hand, the condition can also be controlled and health-related quality of life (HRQoL) maintained for considerable periods (WHO 2011).

Description of the intervention

One of the core pathological features of asthma is considered to be eosinophilic infiltration of the bronchial mucosa, which triggers an inflammatory response. Mepolizumab is a humanised monoclonal antibody against interleukin-5 (IL-5) that has been shown to inhibit eosinophilic airway inflammation. A number of studies have been conducted in young adults (> 12 years old) and adults with recurrent severe asthma exacerbations and signs of eosinophilic inflammation (Haldar 2009; Nair 2009; Pavord 2012). The results of these studies suggest that inhibiting eosinophilic inflammation by monoclonal antibodies may be associated with a reduced risk of acute exacerbations of asthma and a reduction in eosinophil count.

How the intervention might work

Proteins secreted by eosinophils cause damage to the epithelium, initiating vasodilatation, smooth muscle contraction and increased mucous secretion, which in turn is associated with increased airway hyperresponsiveness, asthma symptoms and airway narrowing (Liu 2013).

Mepolizumab is a key monoclonal antibody inhibiting IL-5, which is the main cytokine involved in eosinophil activation and recruitment. This intervention might work by preventing the initiation of the inflammatory response. Mepolizumab is administered intravenously as either a one-off dose of 2.5 to 10 mg/kg or monthly doses of 75 mg, 250 mg or 750 mg given for a period ranging from 16 to 52 weeks. Mepolizumab can also be given subcutaneously.

Why it is important to do this review

In a recently published meta-analysis of seven randomised placebo-controlled trials on 1131 adults, mepolizumab was shown to reduce the risk of exacerbations and improve quality of life in people with eosinophilic asthma, but did not lead to a significant improvement in lung function (Liu 2013).

It is important to do this review so that the evidence presented and the judgements made in Liu 2013 are available and placed in context within *The Cochrane Library*. Our review will also set the stage for future updates as more evidence becomes available.

Objectives

To compare the effects of mepolizumab with placebo on exacerbations and HRQoL in adults and children with chronic asthma.

Methods

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs). We included studies reported as full text, those published as abstracts only and unpublished data. Included trials were a minimum of 16 weeks in duration.

Types of participants

We included both adults and children with a diagnosis of asthma. We focused on collating data from people who have been reported as having eosinophilic asthma to analyse these individuals as a subgroup. We examined individual articles in order to determine how this group should be defined.

Individuals with congential heart disease and respiratory comorbidities such as cystic fibrosis were excluded, as were current smokers.

Types of interventions

We included trials comparing mepolizumab with placebo. We planned to include the following cointerventions provided they were not part of the randomised treatment: leukotriene antagonists, inhaled bronchodilators (including long-acting $beta_2$-agonists), systemic and inhaled steroids, oral aminophylline and macrolide antibiotics.

Studies that initiated a reduction in standard asthma management as part of the protocol were excluded. Nair 2009 included a reduction in the dose of prednisolone in the second phase of the trial. Therefore, only phase one of this trial was included as patients remained on their standard asthma treatment during this four-week period.

Types of outcome measures

Primary outcomes

1. HRQoL (as measured by a validated questionnaire)
2. Asthma exacerbation as defined by a hospital admission or treatment with a course of oral corticosteroids
3. Serious adverse events

Secondary outcomes

1. Measures of lung function: forced expiratory flow in one second (FEV_1), peak expiratory flow rate (PEFR)
2. Asthma symptoms
3. Adverse events/side effects
4. Eosinophil counts in peripheral blood, sputum or bronchioalveolar lavage fluid

Reporting one or more of the outcomes listed here in the trial was not an inclusion criterion for the review.

Search methods for identification of studies

Electronic searches

We identified trials from the Cochrane Airways Group Specialised Register (CAGR), which is maintained by the Trials Search Co-ordinator for the Group. The Register contains trial reports identified through systematic searches of bibliographic databases, including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL, AMED and PsycINFO. We also handsearched respiratory journals and meeting abstracts (please see Appendix 1 for further details). We searched all records in the CAGR using the search strategy in Appendix 2.

We also conducted a search of ClinicalTrials.gov (www.clinicaltrials.gov) and the World Health Organization (WHO) trials portal (www.who.int/ictrp/en/).

We searched all databases from their inception to the present and imposed no restriction on language of publication. The search was first conducted in November 2013 and was updated in November 2014.

Searching other resources

We checked the bibliographies of all primary studies and review articles for additional references. We searched relevant manufacturers' websites for trial information.

We searched for errata and retractions relevant to the included studies published in full text on PubMed (www.ncbi.nlm.nih.gov/pubmed) and planned to report the date this was done within the review if this was an issue.

Data collection and analysis

Selection of studies

Two¬review authors (NW, CP) independently screened titles and abstracts of all the potential studies identified in the search and coded them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We retrieved the full-text study reports/publications, and two review authors (NW, CP) independently screened the full text and identified studies for inclusion, identifying and recording reasons for excluding the ineligible studies. We planned to resolve any disagreement through discussion or, if required, by consulting¬a third author (SJM); however, this was not necessary. We identified and excluded duplicates and collated multiple reports of the same study so that each study rather than each report was the unit of interest in the review. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram and a 'Characteristics of excluded studies' table.

Data extraction and management

We used a data collection form to record study characteristics and outcome data that had been piloted on at least one study in the review. Two review authors (LB, NW) extracted the following study characteristics from included studies.

1. Methods: study design, total duration of study, details of any run-in period, number of study centres and location, study setting, withdrawals and date of study.
2. Participants: number, mean age, age range, gender, severity of condition, diagnostic criteria, baseline lung function, smoking history, inclusion criteria and exclusion criteria.
3. Interventions: intervention, comparator, concomitant medications and excluded medications.
4. Outcomes: primary and secondary outcomes specified and collected, and time points reported.
5. Notes: funding for trial and notable conflicts of interest of trial authors.

Two review authors (LB, NW) independently extracted outcome data from included studies. We noted in the 'Characteristics of included studies' table if outcome data were not reported in a usable way. We planned to resolve disagreements by consensus or by involving a third author (CP), but this was not necessary. One review author (KD) transferred data into

Review Manager (RevMan). We double-checked that data were entered correctly by comparing the data presented in the systematic review with the study reports. A second review author (SJM) spot-checked study characteristics for accuracy against the trial report.

Assessment of risk of bias in included studies

Two review authors (LB, NW) independently assessed risk of bias for each study using the criteria outlined in the¬*Cochrane Handbook for Systematic Reviews of Interventions*¬(Higgins 2011). We planned to resolve any disagreements by discussion or by involving another author (SJM), but this was not necessary. We assessed the risk of bias according to the domains:

1. random sequence generation;
2. allocation concealment;
3. blinding of participants and personnel;
4. blinding of outcome assessment;
5. incomplete outcome data;
6. selective outcome reporting;
7. other bias.

We graded each potential source of bias as high, low or unclear, and provided a quotation from the study report together with a justification for this judgement in the 'Risk of bias' table. We summarised the risk of bias judgements across different studies for each of the domains listed. We considered blinding separately for different key outcomes where necessary (e.g. for an unblinded outcome assessment, risk of bias for all-cause mortality may be very different than that for a patient-reported pain scale). Where information on risk of bias related to unpublished data or correspondence with a trialist, we noted this in the 'Risk of bias' table.

When considering treatment effects, we took into account the risk of bias for the studies that contributed to that outcome.

We conducted the review according to this published protocol and have reported any deviations from it in the 'Differences between protocol and review' section of the systematic review.

Measures of treatment effect

We analysed dichotomous data as risk ratios and rate ratios and continuous data as mean differences or standardised mean differences, which are presented with 95% confidence intervals. We entered data presented on a scale with a consistent direction of effect. However, on one occasion we had to use the risk ratio as one study had reported this (Haldar 2009).

We have undertaken meta-analyses only where this was meaningful (i.e. if the treatments, participants and underlying clinical question were sufficiently similar for pooling to make sense).

Where multiple trial arms were reported in a single trial (Flood-Page 2007; Pavord 2012), we combined the relevant arms (750 mg, 250 mg, 75 mg in Pavord 2012 and 750 mg, 250 mg in Flood-Page 2007) when appropriate.

In future updates of this review, we will narratively describe skewed data reported as medians and interquartile ranges. Where multiple trial arms are reported in a single trial, we will include only the relevant arms. If two comparisons (e.g. drug A versus placebo and drug B versus placebo) are combined in the same meta-analysis, we will halve the control group to avoid double-counting.

Unit of analysis issues

No cross-over studies or cluster randomised trials were identified for inclusion in this version of the review. If cross-over trials are identified in the future, data from a paired analysis will be sought from the trial report or authors in order to appropriately include data in the review using the inverse variance method. If cluster randomised trials are identified in the future, then analyses will be at the level of the individual while allowing for the clustering in the data by using the intracluster correlation coefficient. If this is not reported in the trial, then it will be imputed from similar studies.

Dealing with missing data

Although unnecessary for this version of the review, we may contact investigators or study sponsors for future versions in order to verify key study characteristics and obtain missing numerical outcome data where possible (e.g. when a study is identified as an abstract only). Where this is not possible, and the missing data are thought to introduce serious bias, we will explore the impact of including such studies in the overall assessment of results by a sensitivity analysis.¬

Assessment of heterogeneity

Statistical heterogeneity between studies was assessed visually by inspection of the forest plots and using the Chi^2 test (a P value < 0.10 was considered significant due to the low power of the test). The I^2 statistic was also calculated; this describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance). Values of I^2 range from 0% to 100%, with 0% representing no heterogeneity and 100% representing considerable heterogeneity.

For this review, heterogeneity as reported using the I^2 statistic was defined as follows.

- 0% to 40%: heterogeneity might not be important.
- 30% to 60%: may represent moderate heterogeneity.
- 50% to 90%: may represent substantial heterogeneity.
- 75% to 100%: considerable heterogeneity.

Assessment of reporting biases

If we are able to pool more than 10 trials for future versions, we will create and examine a funnel plot to explore possible small study biases and publication bias.

Data synthesis

In view of the considerable clinical heterogeneity between the included studies, we used a random-effects model.

Data on outcomes were combined at 6 months and 12 months. Where data for other time points were reported, these were also described.

Subgroup analysis and investigation of heterogeneity

Provided sufficient studies were included, we planned to carry out subgroup analyses according to:

1. age (0 to 5 years, 6 to 16 years, 17 years and older);
2. eosinophilic individuals versus non-eosinophilic individuals; and
3. dose of intervention (posthoc subgroup identified);

using the outcomes:

1. HRQoL; and
2. asthma symptoms.

If more studies are included in the future, we will use the formal test for subgroup interactions in RevMan.

Sensitivity analysis

We planned to carry out the following sensitivity analyses if sufficient studies were included.

1. Excluding studies with an overall high risk of bias.
2. Excluding cross-over trials and cluster randomised trials.

Summary of findings table

We created 'Summary of findings' tables using the following outcomes.

1. HRQoL.
2. Asthma exacerbation as defined by a hospital admission or treatment with a course of oral corticosteroids.
3. Serious adverse events.

We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence as it relates to the studies that contribute data to the meta-analyses for the prespecified outcomes. We used methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) using GRADEpro software. We have justified all decisions to downgrade or upgrade the quality of studies using footnotes, and we have made comments to aid the reader's understanding of the review where necessary.

Results

Description of studies

Results of the search

We identified 154 records in our literature searches: 129 in database searches in November 2013 and a further 25 in November 2014 (Figure 1). Eight studies met our inclusion criteria ('Characteristics of included studies' table), and two others were included in the ongoing studies category ('Characteristics of ongoing studies' table). The eight included studies had 25 records: one for Buttner 2003; seven for Flood-Page 2003, one for Flood-Page 2007, four for Haldar 2009, one for Leckie 2000; five for Nair 2009; two for Ortega 2014 and four for Pavord 2012. The remaining 127 records were excluded for various reasons ('Characteristics of excluded studies' table).

Included studies

We included eight studies ('Characteristics of included studies' table), involving 1707 total participants distributed as follows: Buttner 2003, 19; Flood-Page 2003, 24; Flood-Page 2007, 362; Haldar 2009, 61; Leckie 2000, 24; Nair 2009, 20; Ortega 2014, 576 Pavord 2012, 621. Table 1 compares the design, numbers, interventions and patient groups in the included trials. The severity of asthma among participants varied from mild atopic asthma to persistent eosinophilic asthma with recurrent exacerbations. The mepolizumab was administered exclusively through intravenous route in seven of the studies, with dosage varying from 2.5 mg/kg or 10 mg/kg, or 75 mg, 250 mg and 750 mg with different dosing regimens over a range of treatment periods. Only one study had a subcutaneous (SC) arm, with a dose of 100 mg (Ortega 2014).

Excluded studies

We excluded 127 records from the review. Of these, 119 (94%) were excluded because mepolizumab had not been included in the study, 4 (3%) were excluded because they did not include a placebo arm, another 2 (2%) were excluded because the focus was on steroid reduction, 1 (1%) was non-randomised, and the remaining study (1%) was conducted on healthy participants without a diagnosis of asthma ('Characteristics of excluded studies' table).

Risk of bias in included studies

Details of our risk of bias assessments are available in the 'Characteristics of included studies' table, and a summary of our assessment can be seen in Figure 2 and Figure 3.

Allocation (selection bias)

We deemed only three studies (Nair 2009; Pavord 2012; Ortega 2014) to be at low risk of bias for both random sequence generation and allocation concealment. We judged Haldar 2009 to be at low risk of bias for random sequence generation, but its bias with regard to allocation concealment was unclear. The risk of bias for the remaining four studies (Buttner 2003; Flood-Page 2003; Flood-Page 2007; Leckie 2000) was unclear for both random sequence generation and allocation concealment (Figure 3).

Blinding (performance bias and detection bias)

With regard to performance bias and detection bias, we determined that all eight studies were at low risk of bias (Figure 3).

Incomplete outcome data (attrition bias)

In terms of attrition bias, we considered seven of the studies to be at low risk of bias, while the risk of bias in Buttner 2003 was unclear (Figure 3).

Selective reporting (reporting bias)

One study noted that there was no significant difference in HRQoL but did not provide any data (Flood-Page 2007), so we considered it to be at high risk of bias. We deemed all other studies to be at low risk of bias as there was no apparent evidence of selective reporting.

Effects of interventions

Primary outcomes

HRQoL (as measured by a validated questionnaire)

Three studies (participants = 1044) measured quality of life using the Asthma Quality of Life Questionnaire (AQLQ) (Flood-Page 2007; Haldar 2009; Pavord 2012). One study noted that there was no significant difference but did not provide any data (Flood-Page 2007).

Intravenous mepolizumab versus placebo

Pavord 2012 reported data at 52 weeks for three different dose groups of Intravenous (IV) mepolizumab (75 mg, 250 mg, 750 mg), which we combined and presented as one group. Haldar 2009 reported data at 50 weeks. Combining the two studies, Analysis 1.1 showed a non-significant difference between IV mepolizumab and placebo (MD 0.21, 95% CI −0.01 to 0.44; participants = 682), favouring IV mepolizumab. Our confidence in this result is low, as the mean difference is less the clinical minimally important difference of 0.5 units, and no responder analysis is reported (Summary of findings table 1).

Ortega 2014 measured quality of life using the St. George's Respiratory Questionnaire (SGRQ) and found a significant difference favouring IV mepolizumab over the placebo (MD 6.40, 95% CI 3.15 to 9.65; participants = 382; Analysis 1.2). We only have moderate confidence in this result, as IV delivery is not currently a licenced route of administration for mepolizumab (Summary of findings table 1).

Subcutaneous mepolizumab versus placebo

Ortega 2014 measured quality of life using the St. George's Respiratory Questionnaire (SGRQ) and found a significant difference between subcutaneous (SC) mepolizumab and placebo, in favour of mepolizumab (MD −7.00, 95% CI −10.19 to −3.81; participants = 385; Analysis 2.1). We have moderate confidence in this result from a single study (Summary of findings table 2).

Asthma exacerbation as defined by a hospital admission or treatment with a course of oral corticosteroids

Six studies (participants = 1664) reported on asthma exacerbations (Flood-Page 2003; Flood-Page 2007; Haldar 2009; Nair 2009; Pavord 2012; Ortega 2014). Increase in oral corticosteroids is included in the definition of exacerbation for three studies (Haldar 2009; Ortega 2014; Pavord 2012). Two studies did not include an increase in oral corticosteroids in the definition of exacerbation (Flood-Page 2007; Nair 2009), while one study did not provide a definition of exacerbation (Flood-Page 2003).

IV Mepolizumab versus placebo

Four studies (Flood-Page 2003; Flood-Page 2007; Haldar 2009; Nair 2009) reported the number of patients experiencing an exacerbation. Analysis 1.6, which used a random-effects model, did not show a significant difference between IV mepolizumab and placebo (Risk Ratio 0.67, 95% CI 0.34 to 1.31; participants = 468 I^2 = 59%). Our confidence in this result is low due to the wide confidence intervals (Summary of findings table 1).

Pavord 2012 reported the rate ratio of exacerbations for each of the three different dose groups of IV mepolizumab compared to placebo. Ortega 2014 reported the percentage reduction in the rate ratio for clinically significant exacerbations for 75 mg IV mepolizumab compared to placebo. We combined the results for groups taking the 75 mg dose from these studies, both of which included participants with severe eosinophilic asthma.

Analysis 1.3 shows similar results for the rate of clinically significant exacerbations, which include a course of oral steroids, emergency department (ED) visit or admission. For the 75 mg dose, the rate of ED visits or hospital admissions for people on mepolizumab was half that of the placebo group (rate ratio 0.52, 95% CI 0.43 to 0.64; participants = 690; studies = 2). For the 250 mg dose, the result was similar (rate ratio 0.61, 95% CI 0.46 to 0.81; participants = 307; studies = 1) and also for the

750 mg dose (rate ratio 0.48, 95% CI 0.36 to 0.64; participants = 311; studies = 1). Our confidence in this result is moderate, as IV delivery is not currently a licenced delivery route for mepolizumab (Summary of findings table 1).

Analysis 1.4 shows the rate ratio for the combined results of these two studies in terms of exacerbations requiring hospital admission, and there is not a significant difference for the 75 mg mepolizumab dose (rate ratio 0.61, 95% CI 0.33 to 1.13; participants = 690; studies = 2). The 750 mg IV mepolizumab group compared to placebo showed a reduction in the risk of being admitted to hospital (rate ratio 0.37, 95% CI 0.16 to 0.86; participants = 311; studies = 1). The 250 mg dose did not show a statistically significant reduction (rate ratio 0.65, 95% CI 0.31 to 1.37; participants = 307; studies = 1), but the difference between doses was not significant (test for subgroup differences: Chi^2 = 1.14, degree of freedom (df) = 2 (P = 0.57), I^2 = 0%).

Analysis 1.5 shows the combined results on exacerbations requiring a visit to the ED or hospital admission. For the 75 mg dose, there was a significant reduction in the exacerbation rate for this outcome (rate ratio 0.52, 95% CI 0.31 to 0.87; participants = 690; studies = 2), and although the reduction in rate was similar for the other doses, it did not reach statistical significance (250 mg dose: rate ratio 0.58, 95% CI 0.30 to 1.12; participants = 307; studies = 1; and 750 mg dose: rate ratio 0.52, 95% CI 0.27 to 1.02; participants = 311; studies = 1). Again there was no significant difference between the results according to dose (test for subgroup differences: Chi^2 = 0.08, df = 2 (P = 0.96), I^2 = 0%).

SC Mepolizumab versus placebo

Ortega 2014 also found a reduction in the rate of all of the above types of exacerbations favouring SC mepolizumab in comparison to placebo. Analysis 2.2 shows the results for hospital admission (rate ratio 0.31, 95% CI 0.11 to 0.91; participants = 385; studies = 1). Analysis 2.3 shows the reduction in either ED visits or hospital admission (rate ratio 0.39, 95% CI 0.18 to 0.83; participants = 385; studies = 1). Analysis 2.4 shows the reduction in clinically significant exacerbations (rate ratio 0.47, 95% CI 0.35 to 0.63; participants = 385; studies = 1). We have moderate confidence in these results from a single study (Summary of findings table 2).

Serious adverse events

Five studies (participants = 1640) reported information on serious adverse events.

Nair 2009 stated that there were no serious adverse events, while Pavord 2012 reported that the overall frequency of serious adverse events was similar across treatment groups and that no serious life-threatening anaphylactic reactions were observed; however, three patients in the IV mepolizumab groups died during the study for reasons that the physician investigator judged to be unrelated to the treatment.

Flood-Page 2007 reported nine serious adverse events: four in patients receiving placebo (vertigo, bladder carcinoma, unintended pregnancy and asthma exacerbation), three in patients receiving IV mepolizumab 250 mg (hydrocephalus/cerebrovascular disorder, constipation and gastrointestinal disturbance), and two in patients receiving IV mepolizumab 750 mg (asthma exacerbation). None of these serious adverse events was considered to be related to the study medication, and there were no significant differences between the treatment groups.

Haldar 2009 reported that hospitalisation for asthma was a serious adverse effect for 10% (3/29) of participants in the IV mepolizumab arm and 34% (11/32) in the placebo arm.

Ortega 2014 reported that the incidence of serious adverse events (including asthma-related events) was 7% in the intravenous mepolizumab group, 8% in the subcutaneous mepolizumab group, and 14% in the placebo group.

Analysis 1.7 indicated that there was a significant difference between IV mepolizumab versus placebo (Risk Ratio 0.49, 95% CI 0.30 to 0.80; participants = 1441; studies = 5; I^2 = 0%), favouring IV mepolizumab. Our confidence in this result is moderate, as IV delivery is not currently a licenced route of administration for mepolizumab (Summary of findings table 1).

Secondary outcomes

Measures of lung function: forced expiratory flow in one second (FEV_1), peak expiratory flow rate (PEFR)

Seven studies (participants = 1688) report on lung function (Flood-Page 2003; Flood-Page 2007; Haldar 2009; Leckie 2000; Nair 2009; Pavord 2012; Ortega 2014).

IV Mepolizumab versus placebo

Flood-Page 2003 reported no difference between IV mepolizumab and placebo for median FEV_1 and median PEFR at 12 weeks (Table 2).

Flood-Page 2007 reported mean change from placebo for FEV_1 (L) and PEFR L/min at weeks 12 and 20. Analysis 1.8 indicates there was no significant difference in FEV_1 between IV mepolizumab and placebo at week 20. Analysis 1.9 shows a significant difference for IV mepolizumab 250 mg compared to placebo (MD 13.49; 95% CI 0.71 to 26.27), but not for the 750 mg compared to placebo group (MD 3.42, 95% CI −9.40 to 16.24). However, the test for subgroup difference was not significant (Chi^2 = 1.19, df = 1 (P = 0.280), I^2 = 15.9%).

Haldar 2009 and Nair 2009 reported no significant difference in post-bronchodilator FEV_1 (L) between IV mepolizumab and placebo at one year and six weeks, respectively (Analysis 1.10). Nair 2009 also reported no difference between IV mepolizumab and placebo for percentage predicted FEV_1 after bronchodilation (Analysis 1.11).

Pavord 2012 found no significant difference between any dose of IV mepolizumab and placebo in pre-bronchodilator FEV_1 (mL) at one year (Analysis 1.13).

Leckie 2000 reports no significant difference between IV mepolizumab and placebo in late asthmatic reaction (maximum percentage fall in FEV_1) (Analysis 1.14).

Ortega 2014 reported a statistically significant difference favouring IV mepolizumab for both pre- and post-bronchodilator FEV1 (MD 0.10 L ; 95% CI 0.01 to 0.19); (MD 0.15 L, 95% CI 0.05 to 0.24), (Analysis 1.10; Analysis 1.12).

SC Mepolizumab versus placebo

Ortega 2014 reported a statistically significant difference favouring SC mepolizumab for both pre- and post-bronchodilator FEV_1 (MD 0.10, 95% CI 0.02 to 0.18; participants = 385; studies = 1 and MD 0.14, 95% CI 0.04 to 0.23; respectively) (Analysis 2.5; Analysis 2.6;).

Asthma symptoms

Five studies (participants = 1640) measured asthma symptoms (Flood-Page 2007; Haldar 2009; Nair 2009; Pavord 2012; Ortega 2014).

IV Mepolizumab versus placebo

Flood-Page 2007 reported results at 20 weeks using the asthma summary symptom score. Nair 2009 reported data at 4 weeks using a symptom score, a cough score and the Juniper Asthma Cough Questionnaire (JACQ) score. Haldar 2009 reported data at one year using the visual analogue scale symptom score and a modified Juniper Asthma Control Score. Pavord 2012 reported data using the asthma control questionnaire at one year. Ortega 2014 reported data at 32 weeks using the five-item Asthma Control Questionnaire (ACQ-5).

There were no significant differences between IV mepolizumab at 250 mg or 750 mg and placebo using an asthma symptom score or the JACQ, but there was a significant difference between 75 mg and placebo (MD − 0.30, 95% CI − 0.55 to − 0.04; participants = 690; studies = 2; Analysis 1.15), although test for subgroup difference was again non-significant (Chi^2 = 0.81, df = 2 (P = 0.67), I^2 = 0%).

SC Mepolizumab versus placebo

There was also a statistically significant improvement in symptoms on SC mepolizumab compared to placebo (MD − 0.44, 95% CI − 0.64 to − 0.24; participants = 385; studies = 1); Analysis 2.7). However, there was no responder analysis, and this mean difference is less than the minimal clinically important difference of − 0.5 units.

Adverse events/side effects

Six studies (participants = 1664) reported adverse events (Flood-Page 2003; Flood-Page 2007; Haldar 2009; Nair 2009; Pavord 2012; Ortega 2014).

Flood-Page 2003 reported that all of the 24 volunteers completed the study without reporting adverse events.

Flood-Page 2007 reported that there were no significant differences between the treatment groups for any adverse events reported. The most common adverse events (at least 5% of participants in any treatment group) were upper respiratory tract infection, asthma, headache, rhinitis, bronchitis, sinusitis, viral infection, injury, back pain, nausea and pharyngitis.

Haldar 2009 reported that one patient withdrew due to rash after mepolizumab infusion.

Nair 2009 reported that one patient in the IV mepolizumab group withdrew because of increased shortness of breath, thought to be due to heart failure. One patient in the placebo group died six months after the study because of sudden cardiac arrest; one patient in the IV mepolizumab group reported aches and tiredness when prednisolone was reduced, and one patient in the placebo group had hypoadrenalism when prednisolone was reduced.

Pavord 2012 found that the most frequently reported adverse events were headache (27 (17%) individuals given placebo, 32 (21%) given 75 mg IV mepolizumab, 32 (21%) given 250 mg IV mepolizumab, and 32 (21%) given 750 mg IV mepolizumab) and nasopharyngitis (24 (15%), 34 (22%), 33 (22%), and 29 (19%) for the four groups, respectively). The most frequently reported drug-related adverse event was infusion-related reaction (e.g. non-allergic reactions), which was reported by 10 (6%) patients given placebo, 8 (5%) given 75 mg mepolizumab, 12 (8%) given 250 mg IV mepolizumab, and 19 (12%) given 750 mg IV mepolizumab. Hypersensitivity deemed to be possibly related to investigational product was reported by three patients (2%) given placebo, none given 75 mg IV mepolizumab, one (< 1%) given 250 mg IV mepolizumab, and two (1%) given 750 mg IV mepolizumab.

In the Ortega 2014 study, the overall incidence of adverse events during treatment was similar in the three groups (84% in the IV mepolizumab group, 78% in the SC mepolizumab group, and 83% in the placebo group). The most frequently reported adverse events were nasopharyngitis and headache. The incidence of adverse events that were considered by the study investigators to be related to a study drug was 17% in the IV mepolizumab group, 20% in the SC mepolizumab group, and 16% in the placebo group. The incidence of injection-site reactions was more frequent in the SC mepolizumab group (9%) than in the IV mepolizumab group or the placebo group (3% in each).

Eosinophil counts in peripheral blood, sputum or bronchioalveolar lavage fluid

All eight studies (participants = 1707) report on eosinophil counts (Buttner 2003; Flood-Page 2003; Flood-Page 2007; Haldar 2009; Leckie 2000; Nair 2009; Pavord 2012; Ortega 2014).

Buttner 2003 found that "[a]sthmatic patients received three consecutive intravenous infusions of either IV mepolizumab (250 mg or 750 mg per dose) or placebo at 4-week intervals. Remarkably, almost a complete disappearance of peripheral blood eosinophils was observed after the first infusion. Eosinophil counts remained low or absent until week 24, 12 weeks after the last infusion. In contrast, there were no significant changes in eosinophil counts in the placebo group. The marked fall in peripheral blood eosinophils was accompanied by a significant decrease in ECP concentrations. The kinetics of ECP (serum eosinophil cationic protein) levels resembled the eosinophil counts. These qualitative and quantitative changes were observed in both treatment groups without a significant difference between the 250 and 750 mg dosage."

Flood-Page 2003 found that at four weeks after the first dose of IV mepolizumab, there was a significant decrease in peripheral blood eosinophil counts in the actively treated group when compared with placebo (P = 0.002). This decrease was maintained throughout the dosing period and was still evident at the time of the repeat bronchoscopy and bone marrow aspirate, [at] Week 10 (P = 0.02). There was a median reduction of 100% from baseline of eosinophils in the actively treated group at Weeks 4 and 10 (interquartile range, 67–100%). A return of blood eosinophil counts toward baseline was observed at a mean of 9 weeks after the last dose (range 4–20 weeks, data not shown). IV mepolizumab produces a 79% median reduction in bronchoalveolar lavage fluid (BALF) eosinophils (interquartile range, 42-99%) (P = 0.4 when compared with placebo) (Table 3).

Flood-Page 2007 found a significant reduction in the eosinophil counts in the 250 mg and 750 mg groups at week 1 (P < 0.001). Also, 32 patients gave samples at baseline and week 12; 17 had sputum eosinophils > 3%. There was a significant decrease in both the 250 mg (P = 0.006) and the 750 mg group (P = 0.004), which was also significant when compared to placebo.

Haldar 2009 reports a significant difference between IV mepolizumab and placebo for geometric mean sputum eosinophil percentage during exacerbation, and a sputum eosinophil count > 3% during exacerbation (% of episodes), Table 4. The study also reports, "[T]he geometric mean of eosinophil counts in the blood during the treatment phase, as compared with the baseline value, was reduced by a factor of 6.6 in the mepolizumab group and by a factor of 1.1 in the placebo group, with the changes from baseline differing between the groups by a factor of 6.1 (95% CI, 4.1 to 8.9; P < 0.001)."

Results from Leckie 2000 are presented in Table 5. There was a significant reduction in blood eosinophils pre-allergen challenge in the group given mepolizumab 10 mg/kg. Postinhaled allergen, there was a significant reduction in blood eosinophils in both groups given mepolizumab. There was a dose dependent reduction in sputum eosinophils in both mepolizumab groups. This result reached statistical significance in the 10 mg/kg group.

Ortega 2014 found a significant decrease in both treatment groups in blood eosinophil count.

Results from Nair 2009 can be found in Table 6. In phase 1 of the trial, a single infusion of mepolizumab 750 mg resulted in a reduction in the number of sputum and blood eosinophils.

Pavord 2012 found that compared with placebo, the ratios of geometric means at 52 weeks showed that the drug reduced blood eosinophil counts (ratios of geometric means 0.22, 95% CI 0.18 to 0.27) in individuals given 75 mg mepolizumab (P < 0.0001; ratios of geometric means 0.14; 95% CI 0.12 to 0.18), in those given 250 mg mepolizumab, (P < 0.0001; ratios of geometric means 0.12; 95% CI 0.09 to 0.14) and in those given 750 mg mepolizumab, (P < 0.0001). In the subgroup of 94 participants who had sputum induction, the drug also caused decreases in sputum eosinophil counts compared with placebo (ratio 0.68. 95% CI 0.13 to 3.52), in individuals given 75 mg mepolizumab (P = 0.6429; ratios of geometric means 0.35, 95% CI 0.08 to 1.52), in those given 250 mg mepolizumab (P = 0.1577; 0.12 95% CI 0.02 to 0.56) and in those given 750 mg (P = 0.0082).

Discussion

Summary of main results

Eight studies met our inclusion criteria for this systematic review (Buttner 2003; Flood-Page 2003; Flood-Page 2007; Haldar 2009; Leckie 2000; Nair 2009; Pavord 2012; Ortega 2014). Six studies included adults participants only, while Pavord 2012 and Ortega 2014 included participants aged 12 years and over, with a mean age of around 50 years and no separate reporting of results in adolescents. In total, 1707 people participated.

The results suggest that mepolizumab leads to an improvement in HRQoL and a reduction in asthma exacerbation rates for people with severe eosinophilic asthma randomised to received mepolizumab compared to placebo, with no significant increase in serious adverse events on treatment.

With regard to the secondary outcome measures, mepolizumab did not lead to a significant increase in measures of lung function (FEV_1 or PEFR). There was no significant difference in asthma symptoms using an asthma symptom score or the

JACQ between IV mepolizumab at 250 mg or 750 mg and placebo. However, there was a significant difference between 75 mg IV mepolizumab and placebo (although a non-significant test for subgroup difference) and between SC mepolizumab and placebo, in participants with severe eosinophilic asthma. There were minimal significant adverse events related to mepolizumab, but headache and nasopharyngitis were commonly reported side effects. Due to the variety of dosing regimens and protocols, direct comparison of eosinophil counts in peripheral blood, sputum and bronchoalveolar fluid was not possible.

Peripheral blood eosinophil counts, sputum eosinophil counts and eosinophil counts in bronchoalveolar fluid all showed a significant reduction after treatment with mepolizumab.

There were only two studies that included paediatric patients, down to the age of 12 years old (Ortega 2014; Pavord 2012),

but there was no separate reporting of results in adolescents, so we have insufficient evidence to undertake a subgroup analysis based on age.

Overall completeness and applicability of evidence

Although the precise definition of asthma exacerbation is subject to debate, with the consequent variability in reporting, it is nevertheless considered to be one of the core outcomes to be measured in asthma studies (Fuhlbrigge 2012). We found evidence of a reduction in the rate of clinically significant exacerbations in adults with severe eosinophilic asthma given IV or SC mepolizumab. Health-related quality of life (HRQoL) improved with intervention compared to placebo by a mean of seven units in the single study using SGRQ (Ortega 2014), but the mean change in AQLQ was less than the minimal clinically important difference and was not accompanied by responder analyses. These two primary outcomes are clinically important outcomes for the individual. Secondary outcomes of asthma symptoms scores, cough scores, lung function and airway hyperreactivity were not influenced by mepolizumab. Most studies examined eosinophils, inflammatory markers and mediators using a combination of peripheral blood, sputum and bronchoalveolar lavage and showed reductions in those who received mepolizumab. The clinical relevance of this finding to patients may not be clinically important. There were no studies in children under 12 and only two studies included children aged 12 years or older (but without disaggregating results for the participating adolescents). The asthma population examined in this review was too heterogeneous to draw any conclusions about the general asthma population.

Quality of the evidence

Using the GRADE system, we considered the quality of evidence for IV mepolizumab to be limited, as this is not a licenced delivery route (so we would regard this as indirect evidence). We felt that the HRQoL results were of moderate quality, and further research may have an important effect on the results presented. There was a risk of reporting bias in the assessment of HRQoL for one paper: Flood-Page 2007 noted no significant changes in HRQoL but did not provide any data, thus no data could be included in the meta-analysis. We are aware of the limitations in some of the studies and have detailed them in the results section, Figure 2 and Figure 3. We determined that the risk of performance bias and detection bias based on the blinding processes was low in all eight studies. We also found that selection bias was low in only three studies for both random sequence generation and allocation concealment (Nair 2009; Ortega 2014; Pavord 2012) but unclear in four others (Buttner 2003; Flood-Page 2003; Flood-Page 2007; Leckie 2000). Haldar 2009 had a low risk of bias for random sequence generation, but the risk of bias was unclear with respect to allocation concealment. Publication bias was not formally assessed through the construction of a funnel plot due to the small number of included studies. However, we performed a thorough search strategy, including searching conference abstracts and ongoing studies, in order to identify unpublished studies.

Potential biases in the review process

We acknowledge the potential for publication bias in this review, as it is possible that we failed to identify unpublished trials that may have provided positive or negative outcomes, which in turn could have altered the treatment benefits. However, to the best of our knowledge, we identified a significant number of trials meeting our inclusion criteria through comprehensive and systematic database searches. We tried to address any study selection bias by having two review authors who independently evaluated all the identified studies. We also ensured that the assessment of each trial was consistently in line with the inclusion criteria.

Agreements and disagreements with other studies or reviews

Our review follows on from Liu 2013, which also considered the efficacy of mepolizumab in patients with asthma. The present review includes one extra study (Ortega 2014), and its findings are consistent with Liu 2013. Both reviews highlight the need for further research in this area.

Authors' conclusions

Implications for practice

It is not possible to draw firm conclusions from this review with respect to the role of mepolizumab versus placebo in patients with asthma, due partly to the heterogeneity of the studies.

The currently available studies provide evidence that mepolizumab leads to an improvement in health-related quality of life scores and a reduction of asthma exacerbations in people with severe eosinophilic asthma (Haldar 2009; Nair 2009; Pavord 2012; Ortega 2014). There was also an improvement in asthma symptom scores in subjects with persistent eosinophilic asthma when using subcutaneous mepolizumab and 75 mg mepolizumab intravenously (Ortega 2014). Mepolizumab did not lead to a significant increase in measures of lung function.

Further research is needed to clarify which subgroups of patients with asthma could potentially benefit from this treatment. Dosage, ideal dosing regimens and duration of treatment need to be clarified, as the studies included in this review differed in their protocols. There were only two studies that included children (over the age of 12), and these do not provide sufficient evidence on which to base a recommendation for use. At the present time, larger studies are required to establish the role of mepolizumab in the treatment of asthma.

Implications for research

There needs to be further research on mepolizumab in children, with a focus on the core outcomes of exacerbations and HRQoL but also asthma symptoms and lung function (in children who can perform respiratory function tests).

In adults, the evidence available so far suggests that there is an improvement in HRQoL and frequency of acute

exacerbations in participants with severe eosinophilic asthma. However, there needs to be further research to ascertain the optimum dose and regimen for mepolizumab therapy, as the studies included in this review used a wide range of dosing regimens.

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We would particularly like to acknowledge the excellent support and assistance from Emma Welsh, Liz Stovold and Emma Jackson of the Cochrane Airways Review Group, together with the greatly appreciated guidance from Chris Cates (Cochrane Airways Review Group Co-ordinating Editor). The support provided by librarians Judith Scammel, Jane Appleton and Hilary Garrett at St George's University of London is also greatly appreciated.

We are very grateful to Chris Cates, the Contact Editor who commented critically on the review.

The information provided by Prof Peter Barnes regarding an included study (Leckie 2000) is also much appreciated.

The background and methods section of this review is based on a standard template used by Cochrane Airways Group.

Contributions of authors

SM, KD, NW and CP contributed to the writing of the protocol. NW and CP independently selected trials for the review, NW and LB extracted the data, and KD entered the data into the RevMan file with cross-checking by SM. KD and SM wrote the Results section, and NW, LB, CP, KD and SM coauthored the Discussion and Conclusions.

Declarations of interest

None known.

Differences between protocol and review

We initially planned to use a fixed-effect model for meta-analysis, but we agreed with a peer reviewer who suggested that a random-effects model was more appropriate in view of the substantial clinical heterogeneity between the trials.

Although sufficient studies were not identified to conduct subgroup analyses, a posthoc subgroup analysis of dose of intervention was identified and included for use in a future version of this review.

We have included lung function and asthma symptoms in the summary of findings table as additional outcomes which we believe to be important to people making decisions about this intervention.

Published notes

Characteristics of studies

Characteristics of included studies

Buttner 2003

Methods	Randomised, placebo-controlled, parallel-group trial
Participants	Reported as: "Seven male and 12 female patients with mild or moderate asthma, aged 20–59 yrs (mean 41 yrs), with duration of disease between 1–32 yrs (mean 11 yrs) were investigated. For inclusion, FEV_1 had to be from 50 to 80% of predicted at baseline, with a reversibility of at least 12%. None of the patients suffered from clinical exacerbation, and all patients were on a stable daily dose of up to 1000 mcg beclomethasone dipropionate or a corresponding dose of other inhaled corticosteroids for at least 6 weeks prior to the study. As a symptom reliever salbutamol was allowed if needed. The detailed clinical characterisation of patients revealed no significant difference between the study groups." 5 participants allocated to receive mepolizumab 750 mg, 7 to receive mepolizumab 250 mg and 7 to receive placebo.
Interventions	1 month run-in period to ensure stable disease 3 intravenous doses of either mepolizumab (750 mg), mepolizumab (250 mg) or placebo every 4 weeks with a follow-up period of 3 months
Outcomes	Peripheral blood leukocytes, qualitative and quantitative distribution of eosinophils and lymphocyte subpopulations, frequencies of IL-2, -3, -4, -5, -10, -13, interferon-c-producing CD4 T-cells and serum eosinophil cationic protein (ECP) levels
Notes	6-month multicentre trial in Germany Supported in part by SmithKline Beecham, Harlow, UK

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Method of randomisation not reported
Blinding of participants and personnel (performance bias)	Low risk	Reported as double blind
Blinding of outcome assessment (detection bias)	Low risk	Reported as double blind
Incomplete outcome data (attrition bias)	Unclear risk	Appears to be unreported
Selective reporting (reporting bias)	Low risk	No apparent indication of reporting bias

Flood-Page 2003

Methods	2-centre, double-blind, placebo-controlled, parallel-group study
Participants	Reported as: "Twenty-four people with mild asthma, with a FEV_1 of 70% or more of predicted. Participants were within an 18- to 55-year-old age range. All were atopic (defined by a positive skin prick test to one or more aeroallergen), and all were well controlled with short-acting 2-agonists, without corticosteroids or other anti-inflammatory drugs in the preceding 8 weeks. All participants had a clear history of asthma, demonstrated airway hyperresponsiveness with a PC_{20} to histamine of 4.0 mg/mL or less. All were nonsmokers. Eleven participants received mepolizumab and 13 received placebo." • Age: mepolizumab, median 31 years (range 20 to 53); placebo, median 30 years (range 20 to 52) • Males: mepolizumab, 9; placebo, 8 • Baseline morning PEFR, L/min: mepolizumab, median 433 (range 358 to 585); placebo, median 459.5 (range 368 to 490) • Baseline FEV_1, L/s: mepolizumab, median 3.05 (range 2.55 to 4.85); placebo, median 3.1 (range 1.8 to 5.25) • Baseline FEV_1, % predicted: mepolizumab, median 87.0 (range 71 to 109); placebo, median 80.0 (range 71 to 106)
Interventions	3 Intravenous doses of either 750 mg of mepolizumab or placebo over 20 weeks (at weeks 0, 4 and 8)
Outcomes	Airway eosinophils, bone marrow eosinophils, blood eosinophils, airway hyperresponsiveness, FEV_1 and PEFR
Notes	20-week study conducted at the Royal Brompton and London Chest Hospitals, London UK. Supported by GlaxoSmithKline.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Method of randomisation not reported
Blinding of participants and personnel (performance bias)	Low risk	Reported as double blind
Blinding of outcome assessment (detection bias)	Low risk	Reported as double blind
Incomplete outcome data (attrition bias)	Low risk	All 24 volunteers completed the study without reporting adverse events or asthma exacerbations
Selective reporting (reporting bias)	Low risk	No apparent indication of reporting bias

Flood-Page 2007

Methods	Multicentre, randomised, double-blind, placebo-controlled trial.
Participants	Reported as: "Enrolled into the study were nonsmoking participants, aged 18–55 years, with asthma managed with inhaled corticosteroids (maximum dose of beclomethasone dipropionate (BDP) or equivalent, 1000 mcg/d). The FEV_1 had to be at least 50% and not more than 80% of the predicted value for age, sex, and height with documented $beta_2$-agonist reversibility of at least 12% after administration of 180 mcg of albuterol (salbutamol). The daily symptom score had to be at least 4 (maximum score, 12) during the 7 days preceding the baseline assessment. The principal exclusion criteria to ensure asthma stability and safety before dosing were as follows: an absolute FEV_1 value measured at randomisation (visit 3) that had changed by more than 20% from the value determined at a baseline signs-and-symptoms visit 2 weeks before dosing (visit 2); an upper respiratory tract infection in the 2 weeks before the first visit; use of oral corticosteroids in the 4 weeks before the first visit; or poorly controlled asthma, defined as hospitalisation or an emergency room visit for the treatment of asthma in the 6 weeks before the first visit." • 116 allocated to receive mepolizumab 750 mg (112 completed), 120 to receive mepolizumab 250 mg (110 completed) and 126 to receive placebo (119 completed) • Age (standard deviation (SD)): mepolizumab 750 mg, mean 36.3 years (±10.4), mepolizumab 250 mg, mean 35.8 years (± 40); placebo, mean 36.8 years (± 10) • Males: mepolizumab 750 mg, 60; mepolizumab 250 mg, 52; placebo, 48 • Baseline ICS (beclomethasone) dose (mcg/d) (SD): mepolizumab 750 mg, mean 710 (± 381); mepolizumab 250 mg, mean 720 (± 448); placebo, mean 740 (± 486) • Baseline morning mean PEFR (L/min) (SD): mepolizumab 750 mg, 375.7 (± 88.8); mepolizumab 250 mg 357.9 (± 90.6); placebo, 359.4 (± 90.4) • Baseline mean FEV_1 (L) (SD): mepolizumab 750 mg, 2.51 (±0.58); mepolizumab 250 mg, 2.46 (± 0.56); placebo, 2.39 (± 0.59) • Baseline mean (SD) FEV_1, % predicted: mepolizumab 750 mg, 68.3% (± 8.8%); mepolizumab 250 mg, 68.4% (± 9.6%); placebo, 68.4% (± 8.7%) • Baseline mean (SD) FEV_1 reversibility: mepolizumab 750 mg, 24.5% (± 11.6%); mepolizumab 250 mg, 24.6% (± 12.1%); placebo, 25.1% (± 11.6%)
Interventions	4-week run-in period to ensure stable disease 3 intravenous doses of mepolizumab (750 mg), mepolizumab (250 mg) or placebo (at weeks 0, 4 and 8)
Outcomes	Reported as: "The primary efficacy variable was the change from baseline in domiciliary morning peak expiratory flow rate (PEFR) recorded at weeks 12 and 20. This was recorded as the mean PEFR over the 7 days preceding the treatment period (baseline value) and preceding weeks 12 and 20. The secondary efficacy variables were the changes from baseline of FEV_1, asthma summary symptom scores (the total of the daytime asthma, nighttime asthma, and morning asthma scores), use of rescue medication such as albuterol (salbutamol), quality of life scores, asthma exacerbation rates, and eosinophil counts in blood and sputum."
Notes	20-week multicentre trial at 55 centres in 5 countries (France, Germany, Netherlands, the UK, and the USA) Supported by GlaxoSmithKline.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Method of randomisation not reported
Blinding of participants and personnel (performance bias)	Low risk	Reported as double blind
Blinding of outcome assessment (detection bias)	Low risk	Reported as double blind
Incomplete outcome data (attrition bias)	Low risk	Reported as: "Of the 362 patients randomised into the study, a total of 21 patients (5.8%) were withdrawn. The percentage of patients completing the study was high for all treatment arms. The most common reason for withdrawal during the study was adverse experience (n=10; 2.8%). The percentage of patients who were withdrawn because of adverse experiences was higher among patients receiving placebo (4.0%) and mepolizumab at 250 mg (3.3%) compared with patients receiving mepolizumab at 750 mg (0.9%). A total of 37 patients were randomised to the induced sputum arm of the study, and 3 patients were subsequently withdrawn."
Selective reporting (reporting bias)	High risk	No significant difference in HRQoL and did not provide any data

Haldar 2009

Methods	Randomised, double-blind, placebo-controlled, parallel-group trial
Participants	Participants had refractory eosinophilic asthma and a history of recurrent severe exacerbations. Reported as: "Inclusion criteria were a diagnosis of refractory asthma according to American Thoracic Society criteria, a sputum eosinophil percentage of more than 3% on at least one occasion in the previous 2 years despite high-dose corticosteroid treatment, and at least two exacerbations requiring rescue prednisolone treatment in the previous 12 months. Additional criteria for inclusion were stable treatment requirements and an absence of exacerbations for more than 6 weeks before enrolment in the study. Exclusion criteria were current smoking, serologic evidence of a parasitic infection, a serious coexisting illness, the possibility of conception, and poor adherence to treatment." • Age: mepolixumab, mean 48 (range from 21 to 63); placebo, mean 50 (range from 24 to 72) • Males: mepolixumab, 14; placebo, 18 • Baseline mean (SD) FEV_1, % predicted after bronchodilator use: mepolizumab, 78.1% (± 20.9%); placebo, 77.6% (± 24.1%) • Baseline mean (SD) FEV_1/FVC ratio: mepolizumab, 72.2% (± 9.6%), placebo, 67.7% (± 13.5%) • 29 allocated to receive mepolizumab 750 mg, 32 to receive placebo
Interventions	Intravenous mepolizumab (750 mg) versus matched placebo (150 mL of 0.9% saline) at monthly intervals for 1 year
Outcomes	Reported as: "[P]rimary outcome measure was the number of severe exacerbations per subject during the 50-week treatment phase. Secondary outcomes included a change in asthma symptoms, scores on the Asthma Quality of Life Questionnaire (AQLQ, in which scores range from 1 to 7, with lower values indicating more severe impairment and a change of 0.5 unit considered to be clinically important), forced expiratory volume in 1 second (FEV_1) after use of a bronchodilator, airway hyperresponsiveness, and eosinophil counts in the blood and sputum."
Notes	Single centre trial conducted at Institute for Lung Health, Leicester, UK Supported by GlaxoSmithKline

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Reported as: "Stratified randomisation with use of the minimisation method, which was performed by an independent clinician. Participants were randomly assigned with the use of the minimisation method to receive 12 infusions of either 750 mg of mepolizumab delivered intravenously or matched placebo (150 mL of 0.9% saline) at monthly intervals between visits 3 and 14. The criteria used for minimisation were the frequency of exacerbations in the previous 12 months, the baseline eosinophil count in the sputum and the number of participants taking oral corticosteroids."
Allocation concealment (selection bias)	Unclear risk	Details not reported
Blinding of participants and personnel (performance bias)	Low risk	Reported as double blind
Blinding of outcome assessment (detection bias)	Low risk	Reported as double blind
Incomplete outcome data (attrition bias)	Low risk	Reported as: "A total of 61 of the 63 participants (one required and operation and one withdrew consent) who were screened started treatment and constituted the modified intention-to-treat population. Thirty-two participants were randomly assigned to receive placebo. Overall, 94.9% of treatment visits were completed. Participants who withdrew completed a mean of 4.6 treatment visits (38.3%)."
Selective reporting (reporting bias)	Low risk	No apparent indication of reporting bias

Leckie 2000

Methods	Randomised, double-blind, placebo-controlled trial
Participants	Participants with mild allergic asthma Reported as: "24 non-smoking men (mean age 27, range 18–45 years) with mild allergic asthma (as defined by the American Thoracic Society) and a history of episodic wheeze and shortness of breath. The patients were atopic, as defined by positive skin tests in response to common airborne allergens (*Dermatophagoides pteronyssinus*, mixed grass pollen and cat hair) and were maintained on short-acting inhaled 2-agonist treatment as required. Patients had neither worsening asthma nor a respiratory infection in the preceding 6 weeks. FEV_1 at baseline was at least 70% of the predicted value and there was a documented airway hyperresponsiveness to histamine, with a provocation concentration causing a 20% reduction in FEV_1 (PC_{20}) < 8 mg/mL. Patients had documented early and late asthmatic responses (defined as a 15% reduction in FEV_1 on at least three occasions between 4 and 10 h after allergen) to inhaled incremental allergen challenge between 3 and 6 weeks before the study treatment was given." • Mean age (SD): mepolizumab 10 mg/kg, 28.0 years (± 4.3); mepolizumab 2.5 mg/kg, 30.0 (± 8); placebo, 25.6 (± 4.1) • Males: mepolizumab 10 mg/kg, 8; mepolizumab 2.5 mg/kg, 8; placebo, 8 • Baseline mean (SD) FEV_1, % predicted: mepolizumab 10 mg/kg, 82.0% (± 7.0%); mepolizumab 2.5 mg/kg, 90.3% (± 10.4%); placebo, 93.0% (± 9.6%) • 8 allocated to receive mepolizumab 10 mg/kg (8 completed), 8 allocated to receive mepolizumab 2.5 mg/kg (7 completed) and 8 to receive placebo (8 completed)
Interventions	Mepolizumab 10 mg/kg versus mepolizumab 2.5 mg/kg versus placebo
Outcomes	Blood eosinophils, sputum eosinophils, histamine PC_{20} (mg/mL), late asthmatic reaction (maximum % fall in FEV_1)
Notes	16 week study conducted at 3 centres: Imperial College London, Southampton University and University of Amsterdam Supported by SmithKline Beecham, UK

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Method of randomisation not reported
Blinding of participants and personnel (performance bias)	Low risk	Study reported as double blind
Blinding of outcome assessment (detection bias)	Low risk	Study reported as double blind
Incomplete outcome data (attrition bias)	Low risk	1 subject lost to follow-up, all other data appears to be reported
Selective reporting (reporting bias)	Low risk	No apparent indication of reporting bias

Nair 2009

Methods	Randomised, double-blind, placebo-controlled trial

Participants	Inclusion criteria: Adult patients, aged 18 to 70 years, who were followed as outpatients and who required a minimum dose of prednisone treatment (in addition to high-dose inhaled steroid treatment) to prevent frequent exacerbations associated with induced sputum eosinophilia. Patients were enrolled if, at screening and baseline visits, they demonstrated sputum eosinophilia and symptoms. The symptoms could affect activity and sleep but should not have been severe enough to be of concern to the treating physician. Both FEV_1 (after appropriately withholding bronchodilators before and after inhaled salbutamol 200 mcg) and methacholine PC_{20} were measured, but these did not need to be abnormal since the prednisone was required for the control of eosinophilic bronchitis and any clinical consequences of this, and because bronchitis can occur without these features of asthma. On the same doses of corticosteroids for a least one month. Exclusion criteria: pregnancy, breastfeeding or lack of effective contraception in females of childbearing potential or females who are postmenopausal < 1 year. Baseline predicted FEV_1 before bronchodilator of 40% or less. This lower FEV_1 was acceptable since chronic airflow limitation, secondary to the eosinophilic bronchitis or asthma, is not an exclusion criterion. Neither is current or ex-cigarette smoking provided that the best FEV_1 in these patients was >60% predicted normal, or the best FEV_1/VC ratio was >60% in the previous two years. Exposure to a relevant seasonal environmental allergen, known to worsen asthma control, during the study period. Respiratory tract infection in the 4 weeks before the baseline visit. Clinical exacerbation requiring extra prednisone treatment in the 4 weeks before visit 1. Other cardiac, pulmonary, renal or systemic diseases that in the investigator's opinion could interfere with the study results or compromise participants' safety. Previous participation in any study using anti-monoclonal drug. 9 patients were assigned to receive mepolizumab (administered in 5 monthly infusions of 750 mg each) and 11 patients to receive placebo. • Mean age (SD): mepolizumab, 56.4 years (± 10.9); placebo, 58.2 years (± 7) • Male: mepolizumab, 4; placebo, 8 • Mean (SD) duration of symptoms: mepolizumab, 13.3 years (± 10.3); placebo, 12.5 years (± 9.5) • Baseline mean (SD) FEV_1 previous minimum (L): mepolizumab, 1.4 (± 0.6); placebo, 1.6 (± 0.5) • Baseline mean (SD) FEV_1, % predicted: mepolizumab, 48% (± 17); placebo, 52% (± 13%)
Interventions	5 intravenous doses of either mepolizumab (750 mg) or placebo (administered in 5 monthly infusions)
Outcomes	Primary outcome: The prednisone-sparing effect of mepolizumab versus placebo as indicated by the absolute and percentage dose reduction possible without a clinical exacerbation (as measured by the JACQ in patients with asthma or by Likert symptom scores ± FEV_1 in patients with eosinophilic bronchitis without asthma). Secondary outcome measures: The prednisone-sparing effect of mepolizumab or placebo as indicated by the absolute and percentage dose reduction possible without a clinical exacerbation, as measured by; • % sputum eosinophils; • FEV_1 % predicted and methacholine PC_{20}; • blood eosinophils; • amount of rescue salbutamol used; • time to exacerbation.

Notes	26-week trial at Firestone Institute for Respiratory Health, St. Joseph's Healthcare and Department of Medicine, McMaster University, Hamilton, ON, Canada Supported by an unrestricted educational grant from GlaxoSmithKline

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation codes stratified patients into two groups of 10 according to the daily dose of prednisone they were receiving at the time of enrolment (< 10 mg or ≥ 10 mg). Within each of the two groups, patients were equally divided among those receiving mepolizumab and those receiving placebo. When either group was filled, no additional patients were recruited for that group.
Allocation concealment (selection bias)	Low risk	Randomisation codes were held by the pharmacy department, whose members were unaware of clinical details in the study groups.
Blinding of participants and personnel (performance bias)	Low risk	Reported as double blind
Blinding of outcome assessment (detection bias)	Low risk	Reported as double blind
Incomplete outcome data (attrition bias)	Low risk	Two of the patients were included in the study in error and were therefore excluded from some but not all of the analyses before the randomisation code was broken
Selective reporting (reporting bias)	Low risk	No apparent indication of reporting bias

Ortega 2014

Methods	Randomised, double-blind, double-dummy, phase 3 study

Participants	576 patients with recurrent asthma exacerbations and evidence of eosinophilic inflammation despite high doses of inhaled glucocorticoids to one of three study groups. Inclusion criteria: • Able to give written informed consent prior to participation in the study • At least 12 years of age at visit 1 with a minimum weight of 45kg • A well-documented requirement for regular treatment with high dose ICS in the 12 months prior to visit 1, with or without maintenance oral corticosteroids (OCS) • Current treatment with an additional controller medication, besides ICS, for at least 3 months, or a documented failure in the past 12 months of an additional controller medication for at least 3 successive months • Prior documentation of eosinophilic asthma or high likelihood of eosinophilic asthma • At visit 1, a pre-bronchodilator FEV_1 < 80% (for participants ≥ 18 years of age), a pre-bronchodilator FEV_1 < 90% or FEV_1/FVC ratio < 0.8 (for participants 12 to17 years of age) • Previously confirmed history of two or more exacerbations requiring treatment with systemic corticosteroids • Male or eligible female (females of childbearing potential must commit to consistent and correct use of an acceptable method of birth control) • French participants will be included only if affiliated to or a beneficiary of a social security category Exclusion criteria: • Current smokers or former smokers with a smoking history of ≥ 10 pack-years • Presence of a known pre-existing, clinically important lung condition other than asthma • A current malignancy or previous history of malignancy in previous 12 months • Known, pre-existing, unstable liver disease cirrhosis and known biliary abnormalities • Known, pre-existing severe or clinically significant cardiovascular disease • Known, pre-existing other concurrent clinically significant medical conditions that are uncontrolled with standard treatment • Participants with any eosinophilic diseases • QTc(F)[a] ≥ 450 ms or QTc(F) ≥ 480 ms • A history of alcohol/substance abuse • Known immunodeficiency • Administration of omalizumab within 130 days of visit 1 or any other monoclonal antibody to treat inflammatory disease within 5 half-lives of visit 1 • Treatment with an investigational drug within the previous 30 days or 5 terminal phase half-lives of the drug, whichever is longer • Allergy/intolerance to a monoclonal antibody or biologic therapy • Pregnant or breastfeeding • Known evidence of lack of adherence to controller medications, inability to follow physician's recommendations, or both • Previous participation in any study with mepolizumab and administration of investigational product (including placebo)
Interventions	Mepolizumab in a 75 mg intravenous dose versus mepolizumab in a 100 mg subcutaneous dose versus placebo every 4 weeks for 32 weeks
Outcomes	Primary outcome: • Number of clinically significant exacerbations of asthma per year Secondary outcomes: • Number of clinically significant exacerbations requiring hospitalisation (including intubation and admittance to an intensive care unit) or ED visits per year • Mean change from baseline in clinic pre-bronchodilator FEV_1 at week 32 • Mean change from baseline in the SGRQ total score at week 32
Notes	32-week treatment intervention, with 1 to 6 weeks run-in and 8-week followup. Conducted in Baltimore, Middlesex, Ghent, Vancouver, Parma, Marseille and Paris

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centralised computer-generated permuted block schedule
Allocation concealment (selection bias)	Low risk	Treatment allocations will be concealed via the RandAll system
Blinding of participants and personnel (performance bias)	Low risk	Mepolizumab and placebo were identical in appearance and were administered by a staff member who was unaware of the study group assignments.
Blinding of outcome assessment (detection bias)	Low risk	The study drugs were prepared by staff members who were aware of the study group assignments but were not involved in study assessments.
Incomplete outcome data (attrition bias)	Low risk	6% (placebo), 8% (IV), 5% (SC) did not complete the study
Selective reporting (reporting bias)	Low risk	All outcome measures reported

Pavord 2012

Methods	Multicentre, double-blind, placebo-controlled trial

Participants	People with severe asthma despite receiving high doses of standard asthma medications Inclusion criteria: • Male or female • Aged 12 to 65 years inclusive • Minimum weight 45 kg • Clinical features of severe refractory asthma • Well-documented requirement for high dose ICS(i.e. ≥ 880 mcg/day fluticasone propionate or equivalent daily) for at least 12 months • Use of additional controller medication in addition to high dose ICS for at least 12 months • Persistent airflow obstruction indicated by a pre-bronchodilator FEV_1 < 80% predicted at visit 1 or 2 or peak flow diurnal variability of > 20% on 3 or more days during the run-in • Airway inflammation likely to be eosinophilic in nature, demonstrated by either raised peripheral blood eosinophils (≥ 300/μL), sputum eosinophils (≥ 3%), exhaled nitric oxide (≥50 ppb) or prompt deterioration of asthma control following a ≤ 25% reduction in regular maintenance dose of ICS or OCS • History of ≥ 2 exacerbations requiring systemic corticosteroids in the previous 12 months • Evidence of asthma documented by airway reversibility, airway hyperresponsiveness or airflow variability • ECG assessment demonstrating QTc < 450 ms or QTc < 480 ms for patients with bundle branch block • Liver function tests on surrogate markers for liver disease, demonstrating ALT< 2 x ULN, AST < 2 x ULN, Alk Phos ≤ 1.5 x ULN, bilirubin ≤ 1.5 x ULN • Female of non-child-bearing potential or child-bearing potential with a negative pregnancy test at screening and prepared to use an acceptable method of contraception • Able to give written informed consent • Able to read, comprehend and write at a sufficient level to complete study materials Exclusion Criteria: • Current smokers or smoking history of ≥ 10 pack years • Clinically important lung condition other than asthma • Diagnosis or suspicion of malignancy • Unstable liver disease • Churg-Strauss syndrome • Use of methotrexate, troleandomycin, oral gold, cyclosporine, azathioprine or any experimental anti-inflammatory therapy within 3 months of screening • Administration of omalizumab (Xolair) or any other biological agent for the treatment of inflammatory disease within 6 months of visit 1 • Regular use of OCS or systemic corticosteroids for diseases other than asthma within 12 months; any intra-articular, short-acting intramuscular corticosteroid within 1 month; or intramuscular, long-acting depot corticosteroid within 3 months • Allergy/intolerance to the excipients in the mepolizumab formulation • Administration of any investigational drug in previous 30 days or 5 terminal half-lives, whichever is longer • Pregnant, breastfeeding or planning to become pregnant • Clinically significant disease which is uncontrolled with standard treatment • History of alcohol misuse or substance abuse • Parasitic infestation within previous 6 months • Known immunodeficiency • Unable to follow instructions, use the electronic diary or peak flow meter • Known evidence of lack of adherence to controller medications, inability to follow physician's recommendations, or both • Previous participation in a study of mepolizumab and received study medication within 90 days • 621 patients were randomised: 156 were assigned to 750 mg mepolizumab, 152 to 250 mg mepolizumab, 154 to 75 mg mepolizumab, and 159 to placebo
Interventions	13 total intravenous infusions of mepolizumab (750 mg), mepolizumab (250 mg), mepolizumab (75 mg) or placebo given every 4 weeks

Outcomes	Primary outcome: • Frequency of clinically significant exacerbations of asthma Secondary outcomes: • Time to first clinically significant exacerbation requiring oral or systemic corticosteroids, hospitalisation, and/or ED visits • Frequency of exacerbations requiring hospitalisation (including intubation and admittance to an ICU) or ED visits • Time to first exacerbation requiring hospitalisation or ED visit • Frequency of investigator-defined exacerbations • Time to first investigator-defined exacerbation • Mean change from baseline in clinic pre-bronchodilator FEV_1 over the 52-week treatment period • Mean change from baseline in clinic post-bronchodilator FEV_1 over the 52-week treatment period • Mean change from baseline in ACQ score
Notes	52-week study conducted at 81 centres in 13 countries (Argentina, Australia, Canada, Chile, France, Germany, South Korea, Poland, Romania, Russia, Ukraine, the UK and the USA) Supported by GlaxoSmithKline

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central telephone-based system and computer-generated randomly permuted block schedule stratified by whether treatment with oral corticosteroids was required
Allocation concealment (selection bias)	Low risk	Mepolizumab and placebo were prepared by unmasked site staff who were not involved in study assessments
Blinding of participants and personnel (performance bias)	Low risk	Mepolizumab and placebo were prepared by unmasked site staff who were not involved in study assessments. Both treatments were identical in appearance and were given to patients by a masked member of the site staff
Blinding of outcome assessment (detection bias)	Low risk	Data analysts were masked to treatment allocation
Incomplete outcome data (attrition bias)	Low risk	All patients accounted for with information on reasons for having withdrawn. Some patients not included in results due to 'poor efficacy'
Selective reporting (reporting bias)	Low risk	No apparent indication of reporting bias

Footnotes

ACQ: Asthma Control Questionnaire; **ALT**: alanine aminotransferase; **Alk Phos**: alkaline phosphatase; **AQLQ**: Asthma Quality of Life Questionnaire; **AST**: aspartate aminotransferase; **ECP**: eosinophil cationic protein; **ED**: emergency department; **FEV_1** : Forced expiratory volume in 1 second; **FVC**: forced vital capacity; **HRQoL**: health-related quality of life;

ICS: inhaled corticosteroid; **IL**: interleukin; **IV**: intravenous; **JACQ**: Juniper Asthma Control Questionnaire; **OCS**: oral corticosteroids; **PC_{20}** : histamine provocative concentration causing a 20% drop in FEV_1; **PEFR**: peak expiratory flow rate;

SC: subcutaneous; **SD**: standard deviation; **SGRQ**: St. George's Respiratory Questionnaire; **ULN**: Upper Limit of Normal; **VC**: vital capacity.

[a] **QTc(F)**: a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle, corrected for the heart rate using Fredericia's formula.

Characteristics of excluded studies

Alvarez-Cuesta 1994

Reason for exclusion	Study does not include mepolizumab

Armentia 1992

Reason for exclusion	Study does not include mepolizumab

Ayres 2004

Reason for exclusion	Study does not include mepolizumab

Bel 2014

Reason for exclusion	Focus of trial is on steroid reduction and therefore does not meet our predefined inclusion criteria

Berger 2003

Reason for exclusion	Study does not include mepolizumab

Blanken 2012

Reason for exclusion	Study does not include mepolizumab

Blanken 2013

Reason for exclusion	Study does not include mepolizumab

Boulet 1997

Reason for exclusion	Study does not include mepolizumab

Bousquet 2004

Reason for exclusion	Study does not include mepolizumab

Bousquet 2011

Reason for exclusion	Study does not include mepolizumab

Brown 2007

Reason for exclusion	Study does not include mepolizumab

Bryant 1975

Reason for exclusion	Study does not include mepolizumab

Bryant 1975a

Reason for exclusion	Study does not include mepolizumab

Buhl 2000a

Reason for exclusion	Study does not include mepolizumab

Buhl 2000b

Reason for exclusion	Study does not include mepolizumab

Buhl 2002

Reason for exclusion	Study does not include mepolizumab

Bush 1985

Reason for exclusion	Study does not include mepolizumab

Busse 2001

Reason for exclusion	Study does not include mepolizumab

Busse 2008

Reason for exclusion	Study does not include mepolizumab

Caffarelli 2000

Reason for exclusion	Study does not include mepolizumab

Castro 2010

Reason for exclusion	Does not include Mepolizumab

Castro 2011

Reason for exclusion	Does not include Mepolizumab

Chandra 1989

Reason for exclusion	Study does not include mepolizumab

Chervinsky 2003

Reason for exclusion	Study does not include mepolizumab

Clavel 1998

Reason for exclusion	Study does not include mepolizumab

Corren 2003

Reason for exclusion	Study does not include mepolizumab

Corren 2010

Reason for exclusion	Study does not include mepolizumab

Cullell-Young 2002

Reason for exclusion	Study does not include mepolizumab

De Boever 2014

Reason for exclusion	Study does not include mepolizumab

Djukanovic 2004

Reason for exclusion	Study does not include mepolizumab

Ebner 1989

Reason for exclusion	Study does not include mepolizumab

Eckman 2010

Reason for exclusion	Study does not include mepolizumab

El-Nawawy 2000

Reason for exclusion	Study does not include mepolizumab

Fahy 1997

Reason for exclusion	Study does not include mepolizumab

Fahy 1999

Reason for exclusion	Study does not include mepolizumab

Finn 2003

Reason for exclusion	Study does not include mepolizumab

Frew 1998

Reason for exclusion	Study does not include mepolizumab

Garcia 2013

Reason for exclusion	Study does not include mepolizumab

Gauvreau 2011

Reason for exclusion	Study does not include mepolizumab

Gauvreau 2014a

Reason for exclusion	Study does not include mepolizumab

Gauvreau 2014b

Reason for exclusion	Study does not include mepolizumab

Gauvreau 2014c

Reason for exclusion	Study does not include mepolizumab

Gevaert 2013

Reason for exclusion	Study does not include mepolizumab

Gordon 1972

Reason for exclusion	Study does not include mepolizumab

Greenberg 1991

Reason for exclusion	Study does not include mepolizumab

Han 2009

Reason for exclusion	Study does not include mepolizumab

Hanania 2011

Reason for exclusion	Study does not include mepolizumab

Hanania 2013

Reason for exclusion	Study does not include mepolizumab

Hanania 2014

Reason for exclusion	Study does not include mepolizumab

Hill 1982

Reason for exclusion	Study does not include mepolizumab

Hodsman 2013

Reason for exclusion	Study does not include mepolizumab

Holgate 2004

Reason for exclusion	Study does not include mepolizumab

Hoshino 2012

Reason for exclusion	Study does not include mepolizumab

Humbert 2005

Reason for exclusion	Study does not include mepolizumab

Humbert 2008

Reason for exclusion	Study does not include mepolizumab

Humbert 2009

Reason for exclusion	Study does not include mepolizumab

Jacquemin 1995

Reason for exclusion	Study does not include mepolizumab

Jutel 2005

Reason for exclusion	Study does not include mepolizumab

Kang 1988

Reason for exclusion	Study does not include mepolizumab

Kips 2003

Reason for exclusion	Study does not include mepolizumab

Kon 2001

Reason for exclusion	Study does not include mepolizumab

Kopp 2009

Reason for exclusion	Study does not include mepolizumab

Kopp 2013

Reason for exclusion	Study does not include mepolizumab

Kulus 2010

Reason for exclusion	Study does not include mepolizumab

Lanier 2003

Reason for exclusion	Study does not include mepolizumab

Lanier 2009

Reason for exclusion	Study does not include mepolizumab

Laviolette 2013

Reason for exclusion	Study does not include mepolizumab

Leynadier 2004

Reason for exclusion	Study does not include mepolizumab

Lizaso 2008

Reason for exclusion	Study does not include mepolizumab

Massanari 2009

Reason for exclusion	Study does not include mepolizumab

Massanari 2010

Reason for exclusion	Study does not include mepolizumab

Mathur 2011

Reason for exclusion	Study does not include Mepolizumab

Metzger 1998

Reason for exclusion	Study does not include mepolizumab

Milgrom 1999

Reason for exclusion	Study does not include mepolizumab

Milgrom 2001

Reason for exclusion	Study does not include mepolizumab

Modlin 1977

Reason for exclusion	Study does not include mepolizumab

Moss 1987

Reason for exclusion	Study does not include mepolizumab

Nair 2010

Reason for exclusion	Study does not include mepolizumab

NCT00802438

Reason for exclusion	Non randomised study

NCT01366521

Reason for exclusion	Phase 2 study comparing three doses of Mepolizumab. This trial does not have a placebo arm.

NCT01471327

Reason for exclusion	Focus of study was on tolerability, pharmacokinetics and pharmacodynamics of single dose SB-240563 administered intravenously to Japanese healthy male subjects. Patients with asthma were not included in the study

NCT01691859

Reason for exclusion	This study does not include a placebo group. Multi-centre, open-label, long term safety study with total sample receiving 100 milligrams (mg) mepolizumab administered subcutaneously (no control group).

NCT01842607

Reason for exclusion	This study does not include a placebo group. Multi-centre, open-label, long term safety study with total sample receiving 100 milligrams (mg) mepolizumab administered subcutaneously (no control group).

NCT02135692

Reason for exclusion	This study does not include a placebo group. Multi-center, open-label, long-term study of subcutaneously (SC) administered mepolizumab 100mg in addition to standard of care (SOC), in subjects with severe eosinophilic asthma

NCT02293265

Reason for exclusion	Study does not include mepolizumab (aim of study is to provide a 'reliable description of the severe asthma patient landscape with respect to the potential eligibility for treatment with mepolizumab, omalizumab, and reslizumab'),

Niven 2008

Reason for exclusion	Study does not include mepolizumab

Noga 2003

Reason for exclusion	Study does not include mepolizumab

Noga 2008

Reason for exclusion	Study does not include mepolizumab

Noonan 2013

Reason for exclusion	Study does not include mepolizumab

Oba 2004

Reason for exclusion	Study does not include mepolizumab

Oh 2013

Reason for exclusion	Study does not include mepolizumab

Ohashi 1997

Reason for exclusion	Study does not include mepolizumab

Ohman 1984

Reason for exclusion	Study does not include mepolizumab

Ohta 2009

Reason for exclusion	Study does not include mepolizumab

Ong 2005

Reason for exclusion	Study does not include mepolizumab

Parker 2010

Reason for exclusion	Study does not include mepolizumab

Pauli 1984

Reason for exclusion	Study does not include mepolizumab

Piper 2013

Reason for exclusion	Study does not include mepolizumab

Prieto 2006

Reason for exclusion	Study does not include mepolizumab

Pui 2010

Reason for exclusion	Study does not include mepolizumab

Rose 2009

Reason for exclusion	Study does not include mepolizumab

Sakamoto 1984

Reason for exclusion	Study does not include mepolizumab

Scheerens 2011

Reason for exclusion	Study does not include mepolizumab

Scheerens 2014

Reason for exclusion	Study does not include mepolizumab

Siergiejko 2011

Reason for exclusion	Study does not include mepolizumab

Silk 1998

Reason for exclusion	Study does not include mepolizumab

Silkoff 2004

Reason for exclusion	Study does not include mepolizumab

Simoes 2007

Reason for exclusion	Study does not include mepolizumab

Singh 2010

Reason for exclusion	Study does not include mepolizumab

Slavin 2009

Reason for exclusion	Study does not include mepolizumab

Soler 2001

Reason for exclusion	Study does not include mepolizumab

Sorkness 2013

Reason for exclusion	Does not include Mepolizumab

Sthoeger 2007

Reason for exclusion	Study does not include mepolizumab

Sugaya 1994

Reason for exclusion	Study does not include mepolizumab

Swanson 2014

Reason for exclusion	Study does not include mepolizumab

Szymaniak 1998

Reason for exclusion	Study does not include mepolizumab

Tanaka 1993

Reason for exclusion	Study does not include mepolizumab

Terr 1969

Reason for exclusion	Study does not include mepolizumab

Van Rensen 2009

Reason for exclusion	Study does not include mepolizumab

Vignola 2004

Reason for exclusion	Study does not include mepolizumab

Wark 2003

Reason for exclusion	Study does not include mepolizumab

Wenzel 2009

Reason for exclusion	Study does not include mepolizumab

Wenzel 2013

Reason for exclusion	Study does not include mepolizumab

Zetterstrom 1972

Reason for exclusion	Study does not include mepolizumab

Zhu 2013

Reason for exclusion	Study does not include mepolizumab

Zielen 2013

Reason for exclusion	Study does not include mepolizumab

Footnotes

Characteristics of studies awaiting classification

Footnotes

Characteristics of ongoing studies

NCT01520051 2012

Study name	Mepolizumab treatment for rhinovirus-induced asthma exacerbations (MATERIAL)
Methods	Randomised double blind trial
Participants	Mild allergic asthma patients with viral airway infections Inclusion criteria: • Age: from 18 to 50 years • History of episodic chest tightness and wheezing • Intermittent or mild persistent asthma according to the criteria of the Global Initiative for Asthma • Non-smoking or stopped smoking more than 12 months ago and ≤ 5 pack-years • Clinically stable, no history of exacerbations within 6 weeks prior to the study • Steroid-naïve or those not currently on corticosteroids and who have not taken any corticosteroids by any dosing routes within 2 weeks prior to the study. Occasional usage of inhaled short-acting $beta_2$-agonists as rescue medication is allowed, prior to and during the study • Baseline FEV_1 > 80% of predicted • Airway hyperresponsiveness, indicated by a positive acetyl-beta-methylcholine bromide (MeBr) challenge with PC_{20} < 9.8 mg/mL • Positive skin prick test (SPT) to one or more of the 12 common aeroallergen extracts, defined as a wheal with an average diameter over 3 mm • No other clinically significant abnormality on medical history and clinical examination Exclusion Criteria: • Presence of antibodies directed against RV16 in serum (titre > 4), measured at visit 1 • History of clinical significant hypotensive episodes or symptoms of fainting, dizziness, or light-headedness • Women who are pregnant, lactating or who have a positive urine pregnancy test at visit 1 • Chronic use of any other medication for treatment of lung disease other than short-acting $beta_2$-agonists • Participation in any clinical investigational drug treatment protocol in previous 3 months • Ongoing use of tobacco products of any kind or previous usage with ≥ 6 total pack-years • Concomitant disease or condition which could interfere with the conduct of the study, or for which the treatment might interfere with the conduct of the study, or which would, in the opinion of the investigator, pose an unacceptable risk to the patient • People with young children (< 2 years)
Interventions	3 monthly intravenous infusions of 750 mg versus 3 monthly intravenous infusions with saline
Outcomes	Primary outcome measures: • FEV_1 1 day prior and 6 days after RV16 challenge • Questionnaire to score asthma and common cold complaints during 14 days following viral infection Secondary outcome measures: • Viral load on day 6 after viral infection • Sputum eosinophils before and after mepolizumab infusion • Cell influx in bronchoalveolar lavage fluid 6 days after viral infection • Pro-inflammatory cytokines in bronchoalveolar lavage fluid 6 days after viral infection • Antibody production 6 weeks after infection

Starting date	January 2012
Contact information	Suzanne Bal, Academisch Medisch Centrum - Universiteit van Amsterdam (AMC-UvA)
Notes	

NCT02281318 2014

Study name	A randomised, double-blind, placebo-controlled, parallel-group, multi-centre, 24-week study to evaluate the efficacy and safety of mepolizumab adjunctive therapy in subjects with severe eosinophilic asthma on markers of asthma control
Methods	Multicentre, placebo-controlled, double-blind, parallel-group study
Participants	People with severe eosinophilic asthma. Approximately 780 participants with severe eosinophilic asthma will be screened to ensure the randomisation of 544 participants (272 participants per treatment group) into the study.
Interventions	Mepolizumab 100 mg subcutaneously into the upper arm or thigh every 4 weeks for a period of 24 weeks (total of 6 doses) along with their respective standard care of treatment, versus placebo (0.9% sodium chloride) subcutaneously into the upper arm or thigh every 4 weeks for a period of 24 weeks (total of 6 doses) along with their respective standard care of treatment
Outcomes	Primary Outcome Measure: • Mean change from baseline in St. George's Respiratory Questionnaire (SGRQ) score at week 24 Secondary Outcome Measures: • Mean change from baseline in clinic pre-bronchodilator FEV_1 at week 24 • Percentage of participants achieving a 4 point or greater reduction from baseline in SGRQ score at week 24 • Mean change from baseline in five-item Asthma Control Questionnaire (ACQ-5) score at week 24
Starting date	December 2014
Contact information	US GSK Clinical Trials Call Center: GSKClinicalSupportHD@gsk.com
Notes	Estimated primary completion date: 2016

Footnotes

FEV_1 : Forced expiratory volume in 1 second; **PC_{20}** : histamine provocative concentration causing a 20% drop in FEV_1

Summary of findings tables

1 Intravenous mepolizumab compared to placebo for asthma

IV mepolizumab compared to placebo for asthma
Patient or population: adults with asthma of varying degrees of severity **Settings**: community **Intervention**: intravenous (IV) mepolizumab **Comparison**: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	IV mepolizumab				
Change in HRQoL assessed with AQLQ. Scale from 1 to 7 (higher is better) Follow-up: 52 weeks	The mean change in HRQoL ranged from 0.18 to 0.71 units	The mean change in HRQoL in the intervention group was 0.21 units more (0.01 fewer to 0.44 more)	-	682 (2 RCTs)	⊕⊕⊖⊖ low[a,b]	Trial participants had severe eosinophilic asthma
Change in HRQoL assessed with SGRQ. Scale from: 0 to 100 (lower is better) Follow-up: 32 weeks	The mean change in HRQoL was − 9.0 units	The mean change in HRQoL in the intervention group was 6.4 units lower (3.15 lower to 9.65 lower)	-	382 (1 RCT)	⊕⊕⊕⊖ moderate[a]	Trial participants had severe eosinophilic asthma
Rate of clinically significant exacerbations - 75 mg mepolizumab versus placebo Follow-up: range 32 to 52 weeks	The mean rate of clinically significant exacerbations on placebo was 1 per patient per year[c]	The mean rate of clinically significant exacerbations in the intervention group was 0.48 less per patient per year (0.57 less to 0.46 less)	Rate ratio 0.52 (0.43 to 0.64)	690 (2 studies)	⊕⊕⊕⊖ moderate[a]	Trial participants had severe eosinophilic asthma
Rate of clinically significant exacerbations - 250 mg mepolizumab versus placebo Follow-up: 52 weeks	The mean rate of clinically significant exacerbations on placebo was 0.43 per patient per year	The mean rate of clinically significant exacerbations in the intervention group was 0.17 less per patient per year (0.08 less to 0.23 less)	Rate ratio 0.61 (0.46 to 0.81)	307 (1 study)	⊕⊕⊕⊖ moderate[a]	Trial participants had severe eosinophilic asthma
Rate of clinically significant exacerbations - 750 mg mepolizumab versus placebo Follow-up: 52 weeks	The mean rate of clinically significant exacerbations on placebo was 0.43 per patient per year	The mean rate of clinically significant exacerbations in the intervention group was 0.22 less per patient per year (0.17 less to 0.25 less)	Rate ratio 0.48 (0.36 to 0.64)	311 (1 study)	⊕⊕⊕⊖ moderate[a]	Trial participants had severe eosinophilic asthma
People with one or more exacerbations Follow-up: 20 to 50 weeks	264 per 1000	177 per 1000 (90 to 345)	Risk ratio 0.67 (0.34 to 1.31)	467 (4 studies)	⊕⊕⊖⊖ low[a,d]	Variety of asthma severity in the trials
Serious adverse events Follow-up: 20 to 52 weeks	82 per 1000	40 per 1000 (24 to 65)	Risk ratio 0.49 (0.30 to 0.80)	1441 (5 studies)	⊕⊕⊕⊖ moderate[a]	Variety of asthma severity in the trials

*The basis for the **assumed risk** is the mean control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
AQLQ: Asthma Quality of Life Questionnaire; **CI:** Confidence interval; **HRQoL**: health-related quality of life; **IV**: intravenous; **RCT**: randomised controlled trial; **SGRQ**: St George's Respiratory Questionnaire.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Footnotes

[a]The intravenous route is not currently licenced for mepolizumab; one point deducted for indirectness.

[b]The mean difference is less than the clinical minimally important difference (0.5 units), and no responder analysis is available; one point deducted.

[c]Placebo exacerbation rate per patient per year is the rounded mean of rate in the placebo arm of the two studies (0.43 and 1.75).

[d]Wide confidence interval increases the uncertainty of this outcome; one point deducted.

2 Subcutaneous mepolizumab compared to placebo for asthma

Subcutaneous mepolizumab compared to placebo for asthma

Patient or population: adults with severe eosinophilic asthma
Settings: community
Intervention: subcutaneous (SC) mepolizumab
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	SC mepolizumab				
Change in HRQoL assessed with SGRQ. Scale from: 0 to 100 (lower is better) Follow-up: 32 weeks	The mean HRQoL was −9.0 units	The mean HRQoL - SGRQ in the intervention group was 7 units fewer (10.19 fewer to 3.81 fewer)	-	385 (1 RCT)	⊕⊕⊕⊖ moderate[a]	
Rate of exacerbations requiring admission Follow-up: 32 weeks	The mean rate of exacerbations requiring admission on placebo was 0.10 per patient per year	The mean rate of exacerbations requiring ED visit or admission in the intervention group was 0.07 less per patient per year (0.01 less to 0.09 less)	Rate ratio 0.31 (0.11 to 0.91)	385 (1 RCT)	⊕⊕⊕⊖ moderate[a]	
Rate of exacerbations requiring ED or admission Follow-up: 32 weeks	The mean rate of exacerbations requiring ED or admission on placebo was 0.20 per patient per year	The mean rate of exacerbations requiring ED or admission in the intervention group was 0.12 less per patient per year (0.03 less to 0.16 less)	Rate ratio 0.39 (0.18 to 0.83)	385 (1 RCT)	⊕⊕⊕⊖ moderate[a]	
Rate of clinically significant exacerbations Follow-up: 32 weeks	The mean rate of clinically significant exacerbations on placebo was 1.75 per patient per year	The mean rate of clinically significant exacerbations in the intervention group was 0.93 less per patient per year (0.65 less to 1.14 less)	Rate ratio 0.47 (0.35 to 0.63)	385 (1 RCT)	⊕⊕⊕⊖ moderate[a]	
Asthma symptoms measured on Asthma Control Questionnaire Scale from: 0 to 6 (lower is better)[b] Follow-up: 32 weeks	The mean change in asthma symptoms was −0.5 units	The mean asthma symptoms in the intervention group was 0.44 units fewer (0.64 fewer to 0.24 fewer)	-	385 (1 RCT)	⊕⊕⊕⊖ low[a,c]	

*The basis for the **assumed risk** was the event rate in the placebo arm of the single included study. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **ED**: emergency department; **HRQoL**: health-related quality of life; **RCT**: randomised controlled trial; **SC**: subcutaneous; **SGRQ**: St George's Respiratory Questionnaire.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Footnotes

[a]This finding is from a single study so we do not know how well this will match further research; one point deducted.

[b]The minimal clinically important difference on this scale is 0.5 units.

[c]The mean difference is less than the clinical minimally important difference (0.5 units), and no responder analysis is

available; one point deducted.

Additional tables

1 Comparisons of study characteristics

Study	Design	Baseline Asthma severity	Baseline treatment	SC or IV	Intervention (mepolizumab)	Follow-up	Primary and secondary outcomes	No. participants
Leckie 2000	RCT double-blind, placebo	Mild allergic asthma	SABA as required	IV	10 mg/kg versus 2.5 mg/kg versus placebo	16 weeks	Blood eosinophils, sputum eosinophils, histamine PC_{20} (mg/mL), late asthmatic reaction (maximum % fall in FEV_1)	24
Buttner 2003	RCT parallel group, multicentre double blind	Mild or moderate asthma (FEV_1 50-80% predicted)	1000 mcg BDP or equivalent and stable	IV	Three 750 or 250 mg or placebo every 4 weeks for 6 months	6 months	Blood eosinophil, ECP, interferon-c producing CD4 T-cells	19
Flood-Page 2003	2-centre double-blind, placebo-controlled, parallel-group study	Mild atopic (skin prick positive)¬ asthma (FEV_1 >70% predicted)	SABA as required and no corticosteroids in previous 8 weeks	IV	Three doses of either 750 mg¬ or placebo over 20 weeks (at weeks 0, 4 and 8)	20 weeks	Airway eosinophils, bone marrow eosinophils, blood eosinophils, airway hyperresponsiveness, FEV_1, PEFR	24
Flood-Page 2007	Multicentre, randomised, double-blind, placebo-controlled trial	Moderate asthma (FEV_1 between 50% and 80% predicted)	maximum dose (BDP) or equivalent, 1000 mcg/d	IV	Three doses of either 750 mg or 250 mg or placebo over 20 weeks (at weeks 0, 4 and 8)	20 weeks	Change from baseline morning PEFR recorded at weeks 12 and 20; asthma summary symptom scores; use of rescue medication such as albuterol (salbutamol); quality of life scores; asthma exacerbation rates; eosinophil counts in blood and sputum	362
Nair 2009	Randomised, double-blind, placebo-controlled trial. ¬	Eosinophilic asthma	Prednisolone treatment with high-dose ICS	IV	Five doses of either 750 mg or placebo (administered in 5 monthly infusions) ¬	26 weeks	Juniper ACQ in patients with asthma or by Likert symptom scores $\pm$ FEV_1 in patients with eosinophilic bronchitis without asthma); the prednisone-sparing effect of mepolimuzab or placebo as indicated by the absolute and percentage dose reduction possible without a clinical exacerbation (defined as % sputum eosinophilia, FEV_1 % predicted and methacholine PC_{20}); blood eosinophils; frequency of rescue salbutamol use; time to exacerbation	20

Study	Design	Baseline Asthma severity	Baseline treatment	SC or IV	Intervention (mepolizumab)	Follow-up	Primary and secondary outcomes	No. participants
Haldar 2009	RCT double-blind, placebo, parallel-group	Eosinophilic asthma and exacerbations	Sputum eosinophilia of more than 3% despite high-dose ICS treatment, and at least two exacerbations in previous 12 months	IV	750 mg versus matched placebo (150 mL of 0.9% saline) at monthly intervals for 1 year	50 weeks	Severe exacerbations per person; secondary outcomes included a change in asthma symptoms (AQLQ); FEV_1 after use of a bronchodilator; airway hyperresponsiveness; eosinophil counts in the blood, sputum	61
Pavord 2012	Multicentre, double-blind, placebo-controlled trial ¬	Eosinophilic asthma and exacerbations	High dose ICS (i.e. ≥ 880 mcg/day FP or equivalent daily) for at least 12 months	IV	13 infusions in total given every 4 weeks of 750 mg, 250 mg, 75 mg or placebo¬	52 weeks	Exacerbations; time to first clinically significant exacerbation; frequency of exacerbations requiring hospitalisation; time to first exacerbation requiring hospitalisation or ED visit; mean change from baseline in clinic pre-bronchodilator FEV_1; mean change from baseline in clinic post-bronchodilator FEV_1; mean change from baseline in ACQ score¬	621
Ortega 2014	Randomised, double-blind, double-dummy, phase 3 study	Persistent eosinophilic asthma	High dose ICS in the 12 months prior to visit 1 with or without maintenance OCS	IV and SC	75 mg IV dose versus 100 mg SC dose versus placebo every 4 weeks for 32 weeks	32	Exacerbations per year; mean change from baseline in clinic pre-bronchodilator FEV_1 at week 32; mean change from baseline in the SGRQ total score at week 32	576

Footnotes

ACQ: Asthma Control Questionnaire; **AQLQ**: Asthma Quality of Life Questionnaire; **BDP**: beclomethasone dipropionate; **ECP** : eosinophil cationic protein; **ED**: emergency department; **FEV_1** : Forced expiratory volume in 1 second; **FP**; fluticasone propionate; **ICS**; inhaled corticosteroid; **IV**: intravenous; **PC_{20}** : histamine provocative concentration causing a 20% drop in FEV_1; **PEFR**: peak expiratory flow rate; **RCT**: randomised controlled trial; **SABA**: short-acting beta-agonists; **SC**: subcutaneous; **SGRQ**: St George's Respiratory Questionnaire.

2 Lung function

		Intervention			Control				
Study	Outcome	N	Pre-dose median (IQR)	Post-dose median (IQR)	N	Pre-dose median (IQR)	Post-dose median (IQR)	Median difference	P value (between groups)
Flood-Page 2003	FEV_1 L/s	11	3.05 (2.69 to 3.28)	3.1 (2.82 to3.85)	13	3.1 (2.65 to 3.51)	3.06 (2.65 to 3.45)	0.15	0.22
Flood-Page 2003	Morning PEFR L/min	11	433 (402 to 497)	436 (417 to 503)	12	459.5 (408 to 481)	448 (370 to 490)	21	0.09

Footnotes

FEV_1 : Forced expiratory volume in 1 second; **IQR**: interquartile range; **PEFR**: peak expiratory flow rate

3 Eosinophils from Flood-Page 2003

Outcome	Intervention			Control			P value
	N	Pre-dose median (IQR)	Post-dose median (IQR)	N	Pre-dose median (IQR)	Post-dose median (IQR)	
BALF (% cell type on cytospin) Eosinophils	11	1.4 (0.9 to 10.2)	0.3 (0.01 to 0.8)	13	1.2 (0.2 to 6)	1.2 (0.3 to 1.6)	0.4

Footnotes

BALF: bronchoalveolar lavage fluid; **IQR**: interquartile range

4 Eosinophils from Haldar 2009

Outcome	Intervention		Control		
	N	Percentage	N	Percentage	P value
Geometric mean sputum eosinophil % during exacerbation	29	1.5%	32	4.4%	0.005
Sputum eosinophil count >3% during exacerbation (% of episodes)	29	36%	32	59%	0.04

Footnotes

5 Sputum eosinophil results from Leckie 2000

		Intervention Mepolizumab (10 mg/kg) N=8	Intervention Mepolizumab (2.5 mg/kg) N=7
Outcome	**Day**	**Difference (95%CI)**	**Difference**
Difference in blood eosinophils vs placebo pre-allergen	Day −14	0.08 (− 0.09 to 0.26), P = 0.4960	0.18 (0.01 to 0.36), P = 0.0292
	Day 8	0.17 (0.04 to 0.30), P = 0.0054	0.01 (− 0.16 to 0.19), P = 1.00
	Day 29	0.21 (0.10 to 0.33), P < 0.0001	0.02 (− 0.14 to 0.18), P = 1.00
Difference in blood eosinophils vs placebo post-allergen	Day −13	0.38 (0.07 to 0.69), P = 0.0144	0.23 (− 0.11 to 0.58), P = 0.2136
	Day 9	0.34 (0.13 to 0.55), P = 0.0006	0.32 (0.11 to 0.53), P = 0.0012
	Day 30	0.49 (0.28 to 0.7), P < 0.0001	0.43 (0.22 to 0.65), P = 0.0002
Difference in sputum eosinophils vs placebo	Day -13	− 2.0 (− 16.2 to 12.3), P = 1.00	− 2.1 (− 16.3 to 12.2), P = 1.00
	Day 9	11.3 (2.6 to 20.1), P = 0.0076	5.0 (− 5.9 to 16.0), P = 0.6108
	Day 30	12.1 (3.1 to − 21.0), P = 0.0050	5.9 (− 5.0 to 16.8), P = 0.4454

Footnotes

6 Sputum eosinophil results from Nair 2009

Outcome	Visit	Intervention		Control		P value
		N	median (range)	N	median (range)	
Sputum eosinophils (%) median	Visit 1	9	16.6 (1.6 to 54.3)	11	4.0 (0 to 35.3)	P < 0.05 compared to baseline
	4 weeks after first dose	9	0 (range 0 to 4.0)	10	3.0 (0 to 16.3)	P < 0.05 compared to baseline
			mean (SD)		mean (SD)	
Blood eosinophils (x 10^9/L)	Visit 1	9	664.4 (492.5)	11	352.1 (± 253.7)	P < 0.05 compared to baseline
	4 weeks after first dose	9	49.5 (37.5)	10	295.8 (± 207.4)	P < 0.05 compared to baseline

Footnotes

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Classification pending references

Data and analyses

1 IV Mepolizumab versus placebo

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1 Health-related quality of life (AQLQ)	2		Mean Difference(IV, Random, 95% CI)	Subtotals only
1.1.1 AQLQ	2	677	Mean Difference(IV, Random, 95% CI)	0.21[-0.01, 0.44]
1.2 Health-related quality of life (SGRQ)	1		Mean Difference(IV, Random, 95% CI)	Subtotals only
1.2.1 SGRQ	1		Mean Difference(IV, Random, 95% CI)	-6.40[-9.65, -3.15]

1.3 Rate of clinically significant exacerbations	2		Rate Ratio(IV, Random, 95% CI)	Subtotals only
1.3.1 75 mg mepolizumab versus placebo	2	690	Rate Ratio(IV, Random, 95% CI)	0.52[0.43, 0.64]
1.3.2 250 mg mepolizumab versus placebo	1	307	Rate Ratio(IV, Random, 95% CI)	0.61[0.46, 0.81]
1.3.3 750 mg mepolizumab versus placebo	1	311	Rate Ratio(IV, Random, 95% CI)	0.48[0.36, 0.64]
1.4 Rate of exacerbations requiring admission	2		Rate Ratio(IV, Random, 95% CI)	Subtotals only
1.4.1 75 mg mepolizumab versus placebo	2	690	Rate Ratio(IV, Random, 95% CI)	0.61[0.33, 1.13]
1.4.2 250 mg mepolizumab versus placebo	1	307	Rate Ratio(IV, Random, 95% CI)	0.65[0.31, 1.37]
1.4.3 750 mg mepolizumab versus placebo	1	311	Rate Ratio(IV, Random, 95% CI)	0.37[0.16, 0.86]
1.5 Rate of exacerbations requiring ED or admission	2		Rate Ratio(IV, Random, 95% CI)	Subtotals only
1.5.1 75 mg mepolizumab versus placebo	2	690	Rate Ratio(IV, Random, 95% CI)	0.52[0.31, 0.87]
1.5.2 250 mg mepolizumab versus placebo	1	307	Rate Ratio(IV, Random, 95% CI)	0.58[0.30, 1.12]
1.5.3 750 mg mepolizumab versus placebo	1	311	Rate Ratio(IV, Random, 95% CI)	0.52[0.27, 1.02]
1.6 People with one or more exacerbations	4	467	Risk Ratio(M-H, Random, 95% CI)	0.67[0.34, 1.31]
1.7 Serious adverse events	5	1441	Risk Ratio(M-H, Random, 95% CI)	0.49[0.30, 0.80]
1.8 FEV1 (litres)	1		Mean Difference(IV, Random, 95% CI)	Subtotals only
1.8.1 250 mg mepolizumab versus placebo	1	246	Mean Difference(IV, Random, 95% CI)	-0.03[-0.13, 0.07]
1.8.2 750 mg mepolizumab versus placebo	1	242	Mean Difference(IV, Random, 95% CI)	0.02[-0.10, 0.14]
1.9 PEFR (L/min)	1		Mean Difference(IV, Random, 95% CI)	Subtotals only
1.9.1 250 mg mepolizumab versus placebo	1	246	Mean Difference(IV, Random, 95% CI)	13.49[0.71, 26.27]
1.9.2 750 mg mepolizumab versus placebo	1	242	Mean Difference(IV, Random, 95% CI)	3.42[-9.40, 16.24]
1.10 Post bronchodilator FEV_1 (L)	3		Mean Difference(IV, Random, 95% CI)	No totals
1.10.1 6 weeks	1		Mean Difference(IV, Random, 95% CI)	No totals
1.10.2 32 weeks	1		Mean Difference(IV, Random, 95% CI)	No totals
1.10.3 1 year	1		Mean Difference(IV, Random, 95% CI)	No totals
1.11 Percentage predicted FEV_1 after bronchodilation	1		Mean Difference(IV, Random, 95% CI)	No totals
1.11.1 6 weeks	1		Mean Difference(IV, Random, 95% CI)	No totals
1.12 Pre-bronchodilator FEV_1 (L) at week 32	1		Mean Difference(IV, Random, 95% CI)	No totals
1.12.1 75 mg mepolizumab versus placebo	1		Mean Difference(IV, Random, 95% CI)	No totals

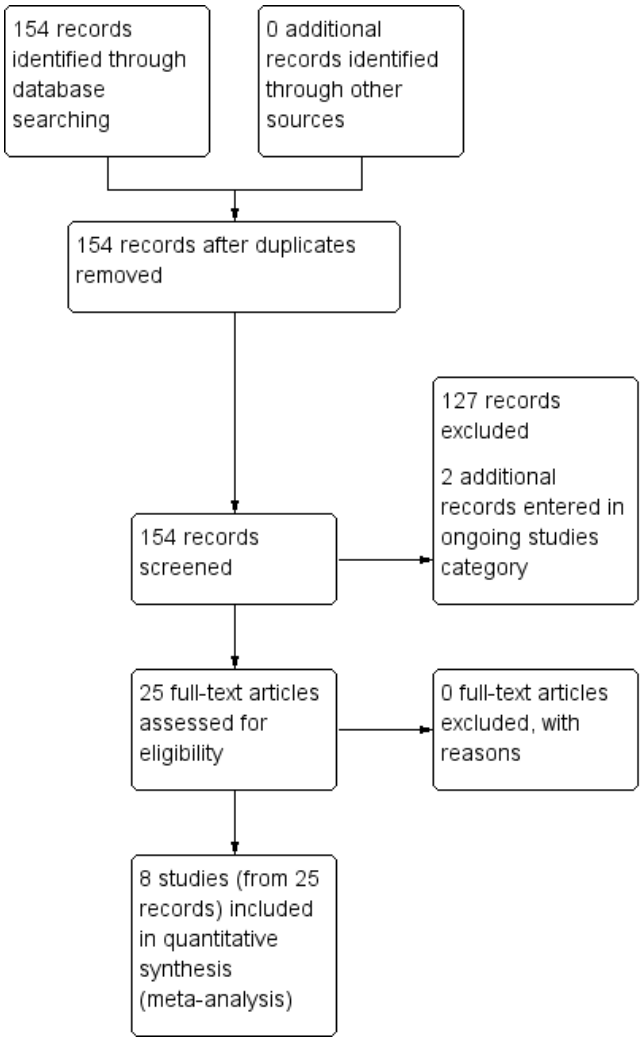
1.13 Pre-bronchodilator FEV_1 (mL) at week 52	1		Mean Difference(IV, Random, 95% CI)	Subtotals only
1.13.1 75 mg mepolizumab versus placebo	1	308	Mean Difference(IV, Random, 95% CI)	61.00[-39.00, 161.00]
1.13.2 250 mg mepolizumab versus placebo	1	307	Mean Difference(IV, Random, 95% CI)	81.00[-18.51, 180.51]
1.13.3 750 mg mepolizumab versus placebo	1	311	Mean Difference(IV, Random, 95% CI)	56.00[-43.00, 155.00]
1.14 Late asthmatic reaction (maximum % fall in FEV1)	1		Mean Difference(IV, Random, 95% CI)	Subtotals only
1.14.1 2.5 mg/kg mepolizumab versus placebo	1	16	Mean Difference(IV, Random, 95% CI)	3.50[-3.46, 10.46]
1.14.2 7.5 mg/kg mepolizumab versus placebo	1	16	Mean Difference(IV, Random, 95% CI)	0.30[-6.50, 7.10]
1.15 Asthma symptoms	5		Mean Difference(IV, Random, 95% CI)	Subtotals only
1.15.1 75 mg mepolizumab versus placebo	2	690	Mean Difference(IV, Random, 95% CI)	-0.30[-0.55, -0.04]
1.15.2 250 mg mepolizumab versus placebo	2	553	Mean Difference(IV, Random, 95% CI)	-0.24[-0.48, 0.01]
1.15.3 750 mg mepolizumab versus placebo	4	631	Mean Difference(IV, Random, 95% CI)	-0.02[-0.57, 0.54]
1.16 Asthma symptoms (JACQ)	2	80	Mean Difference(IV, Random, 95% CI)	-0.04[-0.42, 0.35]

2 SC Mepolizumab versus placebo

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
2.1 Health-related quality of life	1		Mean Difference(IV, Random, 95% CI)	No totals
2.1.1 SGRQ	1		Mean Difference(IV, Random, 95% CI)	No totals
2.2 Rate of exacerbations requiring admission	1		Rate Ratio(IV, Random, 95% CI)	No totals
2.3 Rate of exacerbations requiring ED or admission	1		Rate Ratio(IV, Random, 95% CI)	No totals
2.4 Rate of clinically significant exacerbations	1		Rate Ratio(IV, Random, 95% CI)	No totals
2.5 Pre bronchodilator FEV_1 (litres)	1		Mean Difference(IV, Random, 95% CI)	No totals
2.5.1 32 weeks	1		Mean Difference(IV, Random, 95% CI)	No totals
2.6 Post bronchodilator FEV_1 (litres)	1		Mean Difference(IV, Random, 95% CI)	No totals
2.6.1 32 weeks	1		Mean Difference(IV, Random, 95% CI)	No totals
2.7 Asthma symptoms	1		Mean Difference(IV, Random, 95% CI)	No totals

Figures

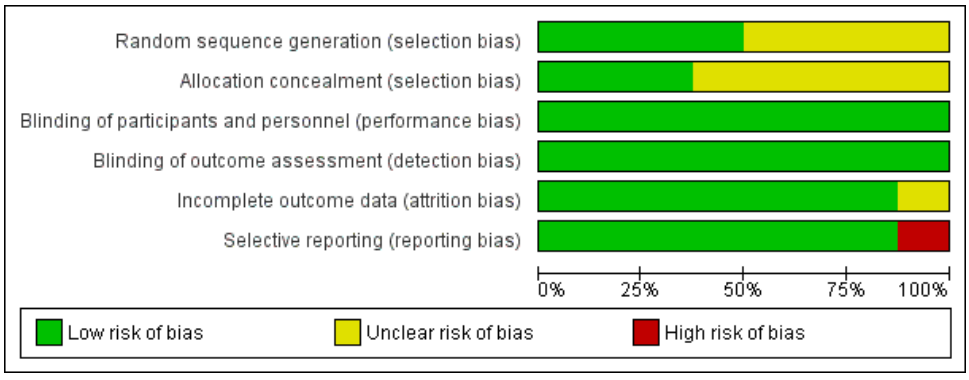
Figure 1



Caption

Study flow diagram

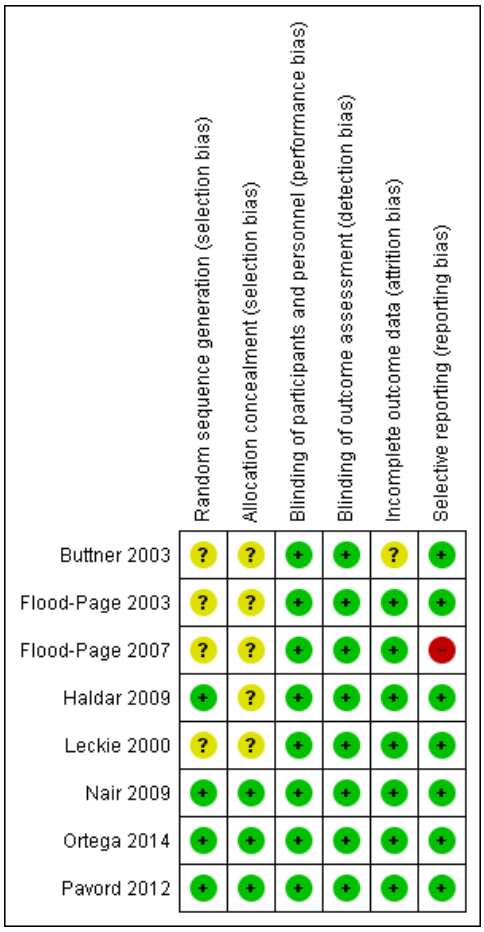
Figure 2



Caption

Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure 3



Caption

Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Sources of support

Internal sources

- No sources of support provided

External sources

- National Institute for Health Research (SJM), UK

Feedback

Appendices

1 Sources and search methods for the Cochrane Airways Group Specialised Register (CAGR)

Electronic searches: core databases

Database	Frequency of search
CENTRAL (*the Cochrane Library*)	Monthly
MEDLINE (Ovid)	Weekly
EMBASE (Ovid)	Weekly
PsycINFO (Ovid)	Monthly
CINAHL (EBSCO)	Monthly
AMED (EBSCO)	Monthly

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Hand-searches: core respiratory conference abstracts

Conference	Years searched
American Academy of Allergy, Asthma and Immunology (AAAAI)	2001 onwards
American Thoracic Society (ATS)	2001 onwards
Asia Pacific Society of Respirology (APSR)	2004 onwards
British Thoracic Society Winter Meeting (BTS)	2000 onwards
Chest Meeting	2003 onwards
European Respiratory Society (ERS)	1992, 1994, 2000 onwards
International Primary Care Respiratory Group Congress (IPCRG)	2002 onwards
Thoracic Society of Australia and New Zealand (TSANZ)	1999 onwards

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MEDLINE search strategy used to identify trials for the CAGR

Asthma search

1. exp Asthma/
2. asthma$.mp.
3. (antiasthma$ or anti-asthma$).mp.
4. Respiratory Sounds/
5. wheez$.mp.
6. Bronchial Spasm/
7. bronchospas$.mp.
8. (bronch$ adj3 spasm$).mp.
9. bronchoconstrict$.mp.
10. exp Bronchoconstriction/
11. (bronch$ adj3 constrict$).mp.
12. Bronchial Hyperreactivity/
13. Respiratory Hypersensitivity/
14. ((bronchial$ or respiratory or airway$ or lung$) adj3 (hypersensitiv$ or hyperreactiv$ or allerg$ or insufficiency)).mp.
15. ((dust or mite$) adj3 (allerg$ or hypersensitiv$)).mp.
16. or/1-15

Filter to identify RCTs

1. exp "clinical trial [publication type]"/
2. (randomised or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. Animals/
10. Humans/
11. 9 not (9 and 10)
12. 8 not 11

The MEDLINE strategy and RCT filter are adapted to identify trials in other electronic databases.

2 Search Strategy for Cochrane Airways Group Register

#1 AST:MISC1

#2 MeSH DESCRIPTOR Asthma Explode All

#3 asthma*:ti,ab

#4 #1 or #2 or #3

#5 MeSH DESCRIPTOR Antibodies, Monoclonal

#6 MeSH DESCRIPTOR Antibodies, Monoclonal, Humanized

#7 mepolizumab*

#8 SB24056 or SB-24056

#9 human* NEAR2 monoclonal* NEAR2 antibod*

#10 Bosatria

#11 #5 or #6 or #7 or #8 or #9 or #10

#12 #4 and #11

[In search line #1, MISC1 denotes the field where the reference has been coded for condition, in this case, asthma]