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# Comparison of anti-interleukin-5 therapies in patients with severe asthma: global and indirect meta-analyses of randomized placebo-controlled trials

Y. Cabon<sup>1</sup>, N. Molinari<sup>1,2</sup>, G. Marin<sup>1</sup>, I. Vachier<sup>3</sup>, A. S. Gamez<sup>3</sup>, P. Chanez<sup>4</sup> and A. Bourdin<sup>2,3</sup>

<sup>1</sup>Department of Medical Information, Montpellier University Hospital, Montpellier, France, <sup>2</sup>PhyMedExp, INSERM U1046, CNRS UMR 9214, University of Montpellier, Montpellier, France, <sup>3</sup>Department of Respiratory Diseases, Montpellier University Hospital, Montpellier, France and <sup>4</sup>AP HM Marseille, Marseille, France

Clinical  
&  
Experimental  
Allergy

## Summary

Inconsistent results have been reported regarding IL-5 blockade treatment in asthma. There were no direct between-treatment comparisons. Only differences between each drug and placebo were studied. We identified all RCTs with anti-IL5 treatments for patients with asthma over the 1990–September 2015 period. RCTs were searched on Medline, Cochrane and Embase. At least 50 patients were enrolled in each study. Outcomes considered were exacerbation rate reduction, FEV<sub>1</sub> changes, ACQ-5 improvement, adverse events and serious adverse events. A global meta-analysis was first conducted followed by an indirect comparison of each IL-5-targeting drug: benralizumab, reslizumab and mepolizumab. Further eosinophilic subgroup analysis and sensitivity analysis were also conducted in case of heterogeneity. Ten trials involving 3421 patients were eligible for meta-analysis. IL-5 blockade significantly reduced annual exacerbation rates vs. placebo by 40% [29–50] ( $P < 0.01$ ,  $I^2 = 0.61$ ). ACQ-5 was significantly improved vs. placebo but below the recognized MCID level ( $-0.31$  [ $-0.41$ ,  $-0.21$ ],  $P < 0.01$ ,  $I^2 = 0.11$ ). FEV<sub>1</sub> changes from baseline were improved vs. placebo by 0.09 L [0.05–0.12] ( $P < 0.01$ ,  $I^2 = 0.28$ ). The subgroup analysis identified a slight additional improvement in mean treatment effects in eosinophilic ( $> 300 \text{ mm}^3/\text{L}$ ) patients with severe asthma. Similar patterns and rates of adverse events and severe adverse events were reported with the three drugs. The data interpretations were not affected by the sensitivity analysis. IL-5 blockade appears to be a relevant treatment strategy to improve severe asthma management, particularly for eosinophilic patients. No clear superiority appeared between the drugs when appropriate doses were compared.

Correspondence: Pr Arnaud Bourdin, Department of Respiratory Diseases, Hôpital Arnaud de Villeneuve, CHU Montpellier, F-34295 Montpellier Cedex 5, France.  
E-mail: a-bourdin@chu-montpellier.fr

## Introduction

Severe asthma is a challenging disease as poor levels of asthma control, frequent exacerbations and impaired lung function are associated with poor outcomes [1]. The role of eosinophils has yet to be clarified [2]. Twenty-five years ago, eosinophilic inflammation was reported to be a common inflammation pattern in asthmatic airways [3, 4], but uncertainties arose when negative results were reported with mepolizumab, a monoclonal antibody directed against IL-5 [2]. Concerns about the inclusion criteria used in these first studies were raised – patients included presented with asthma of mild severity and no prior phenotypic identification

was performed. Heterogeneity of severe asthma was then identified, and phenotypic and endotypic studies led to the idea that TH2/non-TH2 inflammation patterns are potential therapeutic targets [5, 6].

IL-5 is a critical cytokine for eosinophil maturation in bone marrow, with recruitment and activation taking place at the inflammation site through the IL-5 receptor [7]. Other TH2 cytokines, such as IL-13, IL-4, IL-9, TSLP, IL-33 and others, are targets currently under development [8]. IgE blockade downstream of these cytokines was an appealing strategy when there was evidence of IgE involvement. Omalizumab was developed and achieved impressive results in severe asthma [9, 10].

Overlaps between phenotypes were then explored, and IgE/eosinophils were seen as different TH2 surrogate markers [11]. Finally, IL-5 again became the focus of clinical trials, but only in eosinophilic patients.

Mepolizumab is a humanized mAb that was initially administered by monthly intravenous (i.v.) infusions [2], while subcutaneous (s.c.) infusion has also been developed and approved. Reslizumab is also a mAb directed against IL-5 tested on the basis of monthly i.v. infusions [12]. Benralizumab does not directly target IL-5, but rather the IL-5 receptor located mostly on eosinophils. Monthly s.c. administrations have also been designed [13, 14].

In evidence-based medicine, meta-analysis is the most effective way to demonstrate a treatment effect. The results are summarized in forest plots, with publication biases highlighted by funnel plots.

We then assessed whether IL-5 blockade was a relevant strategy through a meta-analysis of all anti-IL-5 mAbs tested in severe asthma. Direct face-to-face comparisons between these mAbs would be difficult to conduct as thousands of patients would probably be required in order to observe a significant difference.

Network meta-analysis offers the opportunity to compare treatment effects in the absence of direct comparison when there is a common comparator (usually a placebo arm).

We then compared these different mAbs at their different doses through an indirect network meta-analysis, which made it possible to address safety concerns.

## Methods

A systematic literature review was conducted by two independent reviewers to identify relevant studies focused on asthma trials with mepolizumab, reslizumab and benralizumab treatments. The databases searched were MEDLINE, MEDLINE-IN-PROCESS, EMBASE, the Cochrane CENTRAL Register and PubMed from 1990 to September 2015. Only articles published in English were included. Data were extracted by the two independent reviewers, and the accordance was assessed by a third reviewer.

Of the 11 clinical trials identified, 10 were considered eligible for the meta-analysis, reported in six separate publications and two publications describing two different trials each [13, 15]. This method was applied to compare the three different anti-IL5 mAbs tested at different doses (Fig. 1). The eligible studies reported outcomes relevant for assessment in asthma therapeutic trials: annual exacerbation rates, FEV<sub>1</sub> change from baseline and variations in asthma symptoms assessed by changes in the ACQ-5. They involved 3421 patients [12, 13, 15–20].

A meta-analysis was first conducted to assess the efficacy of the IL-5 blockade strategy overall. Meta-analysis was used to aggregate individual study treatment effect estimates to achieve a single and more accurate treatment effect estimation. Summarized data from each of the included trials were used to conduct the meta-analysis according to Cochrane guidelines. In case of multi-arm studies, group combining methods were used to deal with treatment arm effects according to the Cochrane Handbook [21]. A random effect model was used in case of significant between-trial heterogeneity, as assessed by Cochran's Q and I<sup>2</sup>. The meta-analysis results were expressed as mean differences, and corresponding 95% confidence intervals, for FEV<sub>1</sub> and ACQ-5 between aggregated treatments compared to placebo, and as an exacerbation rate risk ratio. *P*-values indicating significant differences and I<sup>2</sup> are also presented. Standard errors were selected for this meta-analysis to avoid population size weighting effects. Forest and funnels plots were drawn up. An additional sensitivity analysis was conducted to explore the source of heterogeneity.

An indirect network meta-analysis was then performed to compare each anti-IL5 mAb efficacy and safety result using the Bayesian framework according to Cochrane's collaboration guidelines [22]. The models included multi-arm correction. The network meta-analysis was conducted according to PRISMA guidelines, and R-AMSTAR criteria were assessed to check the overall data quality. We selected a random effect model to allow heterogeneity between indirect comparisons according to ISPOR guidelines [23]. Comparison and treatment rankings were assessed by the network.

A hierarchical model using uniform links was applied to normally distributed data (FEV<sub>1</sub> and ACQ-5) and log-normally distributed data (annual exacerbation rates). Adverse and serious adverse events were assessed using a Poisson discrete process with a logarithmic link function.

When studies did not report the effect variability, the corresponding outcomes were excluded from the analysis.

The results were presented as a median [95% credible interval] with respect to the posterior density (for FEV<sub>1</sub> and ACQ-5) or as an exponential of the median [95% credible interval] for exacerbation rates ratios and safety. The median rank probability ( $P_{\text{rank}}$  within the text) of the treatment was also provided. Specifically,  $P_1$  indicates, for one treatment and one outcome, the probability of being the most effective.

The network meta-analysis was conducted using R 3.2.2 and Winbugs version 1.4.3 software [24]. Flat priors were used for estimate initialization. Estimates were analysed once convergence was assessed through at least 100 000 simulations.

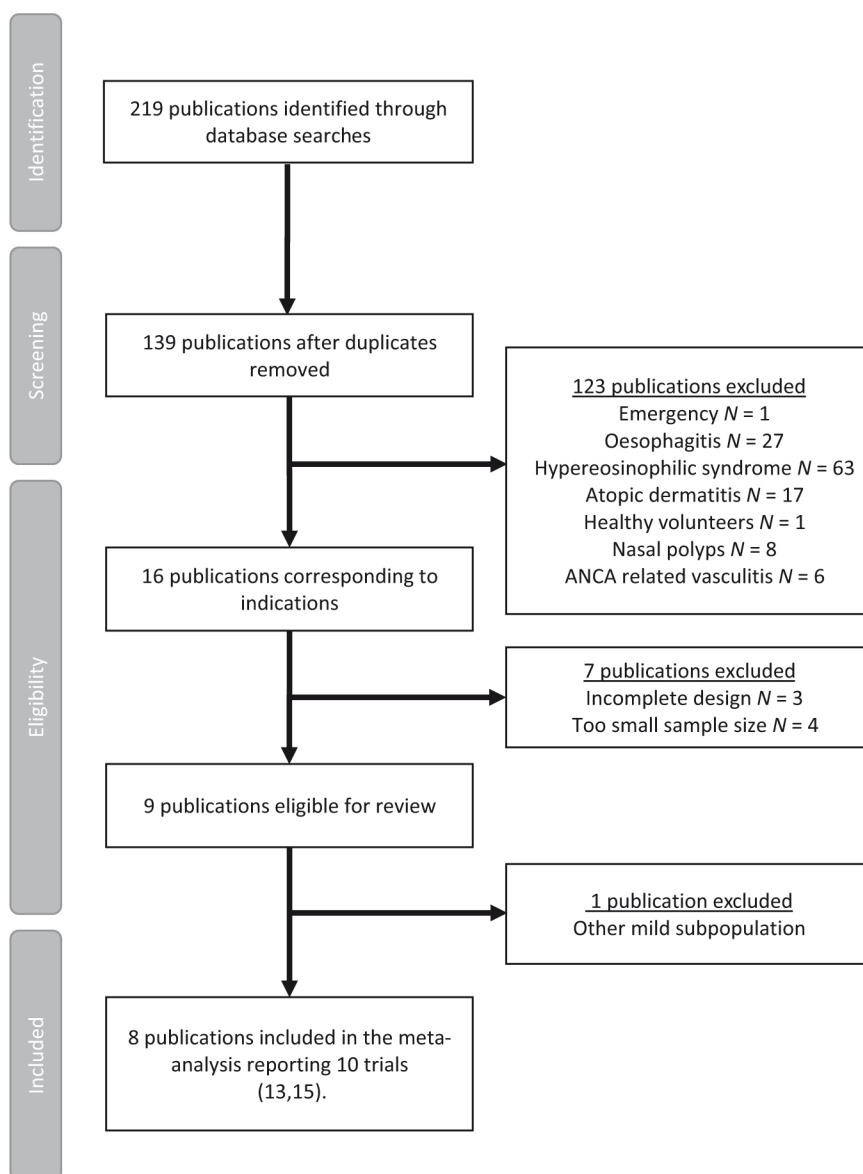


Fig. 1. Study selection flowchart.

The same analysis strategy was applied to the eosinophilic subgroup. The subgroup analysis of the eosinophilic patients was quite complex as the thresholds were defined slightly differently (in the mepolizumab trials, the eosinophilic population was defined by a threshold of 300 eosinophils/mm<sup>3</sup>/L, while a threshold of 400 eosinophils/mm<sup>3</sup>/L was used in the benralizumab and reslizumab trials, and other studies were based on induced sputum eosinophil percentages).

## Results

The defined exacerbation and population characteristics were quite similar in the eight studies consisting of 10 trials, which involved a total of 3421 patients (59.6%

females, average age 47.3 years, average BMI 28.0 kg/m<sup>2</sup>; see details in the Supplementary Appendix). Only randomized, double-blinded, placebo-controlled trials were included. The reference trial numbers and main characteristics are listed in Table 1.

A meta-analysis was performed to assess the overall efficacy of the anti-IL5 strategy. The annual exacerbation rate ratio of the three aggregated anti-IL-5 mAbs vs. placebo was 0.60 [0.50, 0.71],  $P < 0.01$  (Fig. 2). This effect was assessed by a random effect model due to heterogeneity ( $I^2 = 0.61$ ). The FEV<sub>1</sub> change from baseline vs. placebo was 0.09 L [0.05; 0.12],  $P < 0.01$ , using a fixed effect model ( $I^2 = 0.28$ ). The meta-analysis indicated an overall ACQ-5 change from baseline of  $-0.31$  [ $-0.41, -0.21$ ],  $P < 0.01$ , based on a fixed effect model



Table 1. Details of the studies included in the meta-analysis

Trial reference number (publication references)	Quality	Specific design*	Outcome available	Phase	Blood eosinophil count threshold (mm <sup>3</sup> /L)	Number of females (%)	Age (years)	Treatments involved in the studies (number of patients)			
								Treatment 1 (comparator)	Treatment 2	Treatment 3	Treatment 4
Halдар 2009 [20]	Moderate	Parallel group	ER, ACQ, FEV, AE, SAE	–	–	29 (48)	49.0	Plb (33)	Mep750 (29)	–	–
Pavord 2012 [18]	High	Multi-center	ER, ACQ, FEV, SAE	–	> 300	387 (63)	48.6	Plb (159)	Mep75 (153)	Mep250 (152)	Mep750 (156)
Ortega 2014 [17]	High	Double dummy	ER, ACQ, FEV, AE, SAE	III	> 300	329 (57)	50.0	Plb (191)	Mep75 (191)	Mep100 (194)	–
Flood-Page 2007 [19]	High	Parallel group	FEV, SAE	–	–	202 (56)	–	Plb (126)	Mep250 (120)	Mep750 (116)	–
Bel 2014 [16]	Moderate	Parallel group	ER, AE, SAE	–	> 300	74 (55)	28.6	Plb (66)	Mep100 (69)	–	–
Castro 2011 [12]	Moderate	–	ACQ, FEV, AE, SAE	–	–	63 (53)	–	Plb (53)	Res3 (53)	–	–
Castro 2014 [13]	High	Dose ranging, eosinophilic patients	ER, ACQ, FEV, AE <sup>†</sup> , SAE <sup>†</sup>	II b	> 300	219 (69)	28.5	Plb (80)	Ben2 (81)	Ben20 (81)	Ben100 (82)
Castro 2014 [13]	High	Dose ranging, non-eosinophilic patients	ER, ACQ, FEV, AE <sup>†</sup> , SAE <sup>†</sup>	II b	–	198 (70)	29.6	Plb (142)	Ben100 (140)	–	–
Castro 2015 study 1 [15]	High	Parallel group, 128 clinical research centres	ER, ACQ, FEV, AE, SAE	III	> 400	303 (62)	27.8	Plb (244)	Res3 (245)	–	–
Castro 2015 study 2 [15]	High	Multi-center, 104 centres	ER, FEV, AE, SAE	III	> 400	294 (63)	27	Plb (232)	Res3 (232)	–	–

ER, Exacerbation Rate, BMI and age were calculated as means over each arm study. The following abbreviations were used for treatments: Ben represents the benralizumab arm, Mep represents the mepolizumab arm, Plb represents the placebo arm and Res represents the reslizumab arm. Numbers after the abbreviation represent the corresponding dose (2, 20, 100, 75, 250 and 750 mg or 3 mg/kg for reslizumab).

\*All included trials were randomized, double-blinded and placebo-controlled.

<sup>†</sup>AE and SAE were analysed for the overall study and not specifically by trial, as presented in the publications.

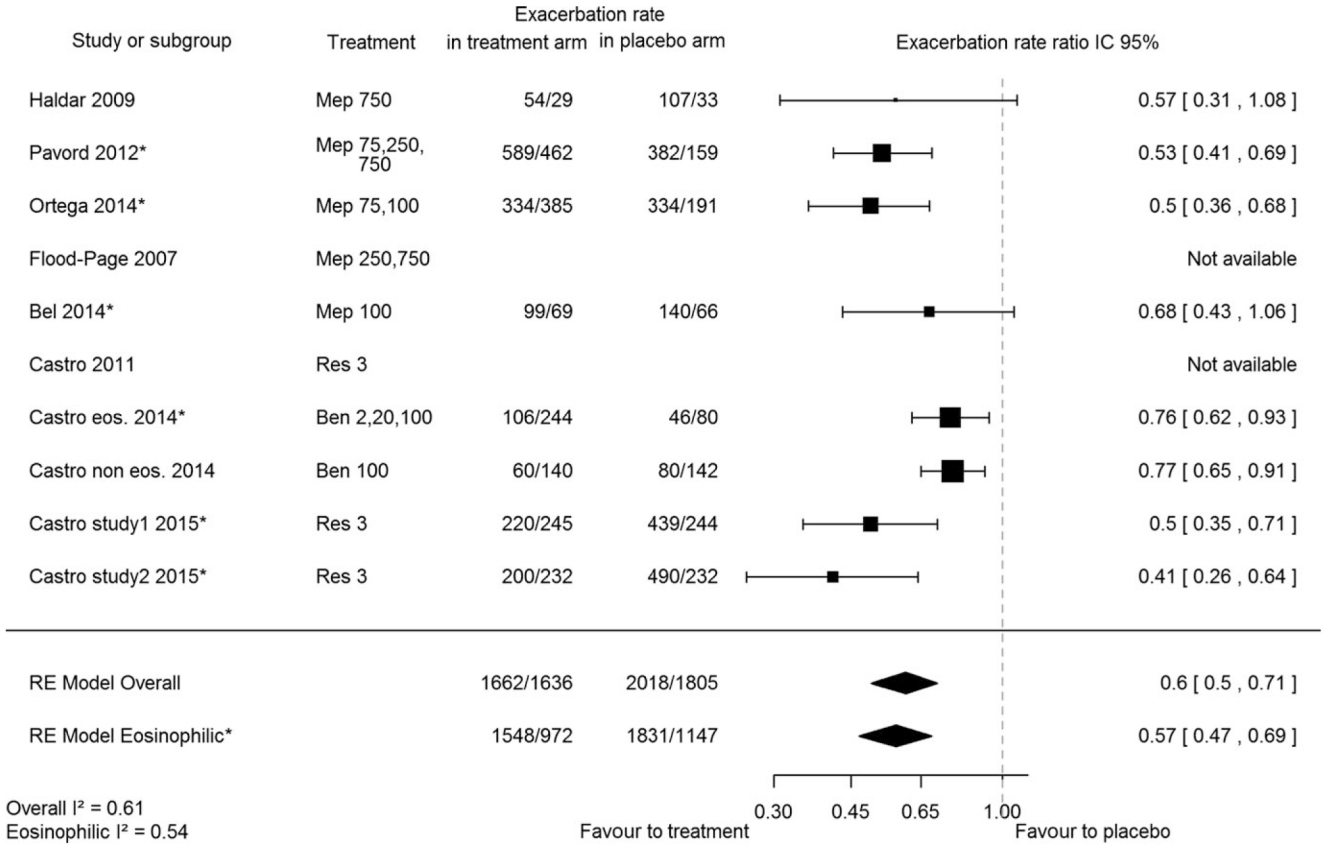


Fig. 2. Forest plot. The eosinophilic subgroup refers to patients enrolled with a blood eosinophilic count at entry  $> 300 \text{ mm}^3/\text{L}$  and was represented by (\*) on this figure.

( $I^2 = 0.11$ ) involving seven studies only, because of missing values in three studies.

The heterogeneity noted in the exacerbation rate ratios was due to the combined rate reduction in eosinophilic and non-eosinophilic 2014 Castro's studies [13]. When these two trials were excluded, the exacerbation rate estimates based on the fixed effect model were 0.52 [0.45, 0.60] ( $P < 0.01$ ,  $I^2 = 0.0$ ).

A specific meta-analysis was performed in the eosinophilic patient subgroup ( $> 300 \text{ mm}^3/\text{L}$ ). For this subgroup, including five studies, the annual exacerbation rate ratio was 0.57 [0.47, 0.69],  $P < 0.01$ ,  $I^2 = 0.54$  (Fig. 2). FEV<sub>1</sub> increased by 0.10 L [0.06, 0.14] ( $P < 0.01$ ,  $I^2 = 0$ ) in this subgroup. ACQ-5 changed by -0.33 [-0.45, -0.21] ( $P < 0.01$ ,  $I^2 = 0.21$ ). The corresponding funnel and forest plots are provided in the Supplementary Appendix.

The combined treatment effect from eosinophilic 2014 Castro's study [13] was a source of heterogeneity. When this study was excluded, the exacerbation rate estimates for the eosinophilic subgroup based on the fixed effect model were 0.52 [0.44, 0.60] ( $P < 0.01$ ,  $I^2 = 0.0$ ). A network meta-analysis was performed to assess indirect treatment comparisons (Fig. 3). The

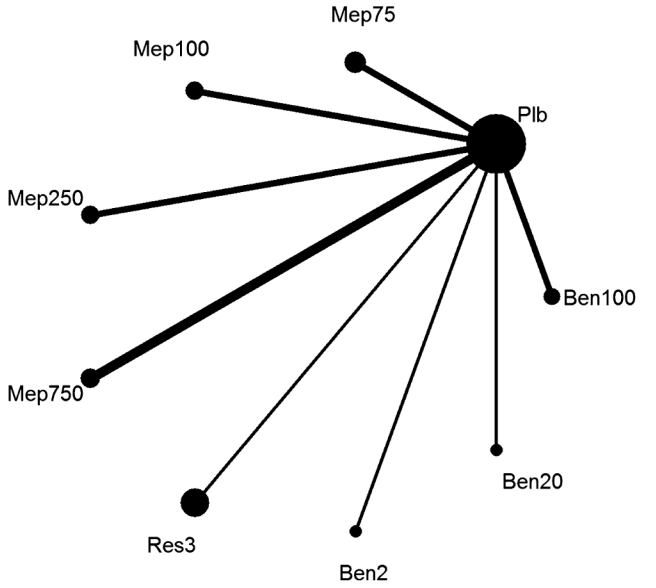


Fig. 3. Network. The line width shown is proportional to the number of comparisons between treatments. The circle size is proportional to the number of patients on the treatment arm.

network displayed all of the included trials vs. placebo, involving four doses of mepolizumab (75 mg i.v., 100 mg s.c., 250 and 750 mg s.c.), one dose of

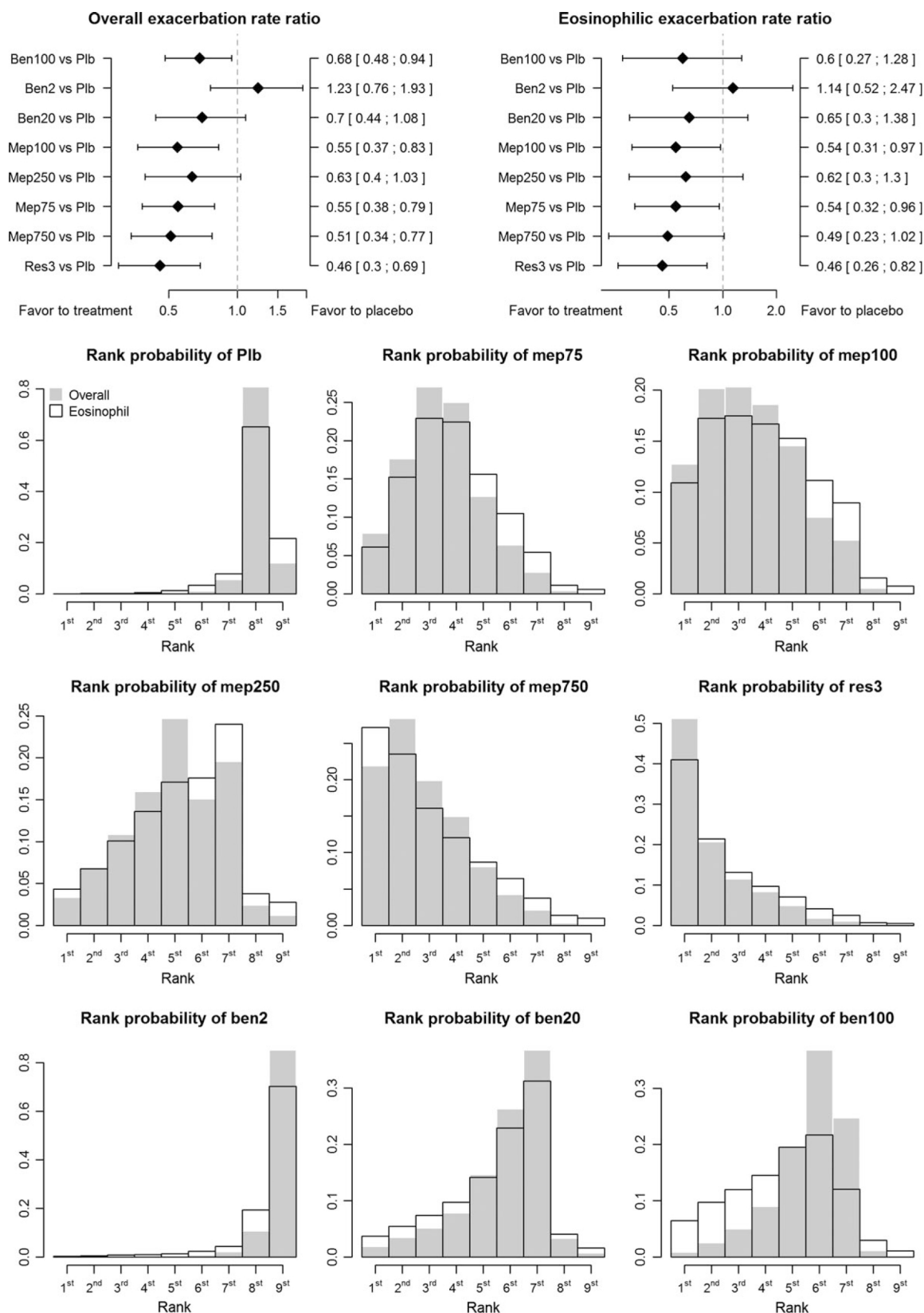


Fig. 4. MTC exacerbation results. The first two forest plots compare exacerbation rate treatment effect vs. placebo. Graphic bars display probabilities of ranking. Y axis is the level of probability of belonging to the class of ranking (given on the X axis), that is  $P_{\text{rank}}$ .

reslizumab (3 mg/kg i.v.) and three doses of benralizumab (2, 20 and 100 mg i.v.).

This network meta-analysis involved sorting all of these arms according to their probability of being ranked first, that is, to provide the greatest benefits (Fig. 4). Accordingly, the top three treatments with the greatest probability of being ranked first for reducing the exacerbation rate were reslizumab 3 mg/kg with  $P_1 = 51\%$ , followed by mepolizumab 750 mg ( $P_1 = 22\%$ ) and mepolizumab 100 mg ( $P_1 = 13\%$ ). Corresponding rate ratio reductions regarding the exacerbation rate vs. placebo were 0.46 [0.3, 0.69] for reslizumab 3 mg/kg, 0.51 [0.35, 0.77] for mepolizumab 750 mg and 0.55 [0.37, 0.83] for mepolizumab 100 mg. As expected, benralizumab 2 mg did not significantly differ from placebo (RR = 1.23 [0.76, 1.93]). Regarding the asthma control questionnaire (ACQ-5) findings, benralizumab 20 mg had the greatest probability of being ranked first (mean difference vs. placebo  $-0.38$  [ $-0.97$ ,  $0.18$ ],  $P_1 = 27\%$ ). Reslizumab 3 mg/kg (0.14 L [ $0.05$ ,  $0.24$ ],  $P_1 = 37\%$ ) had the best likelihood of being ranked first for FEV<sub>1</sub> improvement. Regarding safety concerns (Fig. 5), we analysed non-severe adverse events first. Benralizumab 20 mg had the greatest probability of being ranked as the safest (RR = 0.94 [0.57, 1.54],  $P_1 = 28\%$ ), which was also in favour of the treatment. For severe adverse events, reslizumab was ranked as the best SAE reducer compared to placebo (RR = 0.81 [0.22, 3.03],  $P_1 = 37\%$ ), again in favour of the treatment (Table 2).

In the eosinophilic subgroup, the top three drugs for exacerbation rate reduction were reslizumab 3 mg/kg with a 0.46 [0.26, 0.81] rate ratio regarding the annual exacerbation rate vs. placebo, with a probability of being the best treatment  $P_1 = 41\%$ . This treatment was

followed by mepolizumab 750 mg with 0.49 [0.23, 1.02] ( $P_1 = 27\%$ ) vs. placebo, and then mepolizumab 100 mg with a 0.54 [0.31, 0.97] ( $P_1 = 11\%$ ) rate ratio regarding the annual exacerbation rate vs. placebo. On average, benralizumab 20 mg had the highest probability of being the best treatment for improving the FEV<sub>1</sub> value (0.15L [ $-0.30$ ,  $0.60$ ],  $P_1 = 29\%$ ) and decreasing the ACQ-5 score ( $-0.36$  [ $-2.28$ ,  $1.56$ ],  $P_1 = 18\%$ ). Additional results on treatment effect sizes, forest plots, other rank probabilities and heterogeneity assessments are provided in the Supplementary Appendix. Safety results are also provided in the Supplementary Appendix.

### Discussion

Monoclonal antibodies targeting TH2 cytokines seem to be a good alternative in severe asthma management. In the present meta-analysis based on more than 3000 patients, aggregated anti-IL-5 studies showed a 40% decrease in exacerbation rate. Moreover, FEV<sub>1</sub> was slightly significantly improved by these mAbs, as also were the asthma control levels assessed by the ACQ-5-scores, with the improvement remaining below the minimal clinically important difference (MCID) level [25]. Identification of the high eosinophilic subgroup improved confidence in the overall anti-IL-5 strategy as it increased the homogeneity of population characteristics. Similar results were obtained in the sensitivity analyses. Reslizumab, at the monthly dose of 3 mg/kg, appeared to be the most likely effective treatment for reducing the exacerbation rate. The overall and specific safety profiles appeared to be similar to placebo. Higher AE rates were reported in the reslizumab study, which could potentially be attributed to the administration route.

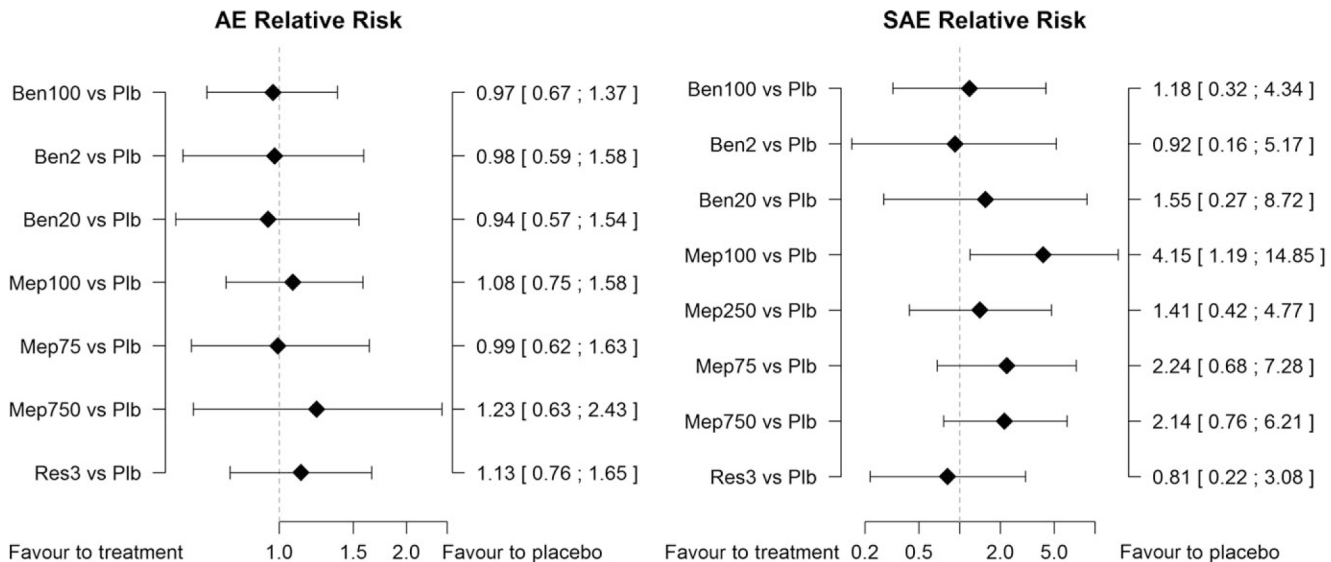


Fig. 5. Network meta-analysis: safety results.



Table 2. Summary of the results

Outcome effect	Treatment		Mepolizumab		Reslizumab		Benralizumab					
	vs. placebo	Dose	75 mg	100 mg	250 mg	750 mg	3 mg/kg	2 mg	20 mg	100 mg		
Overall												
Exacerbation rate*	–		0.55 [0.38, 0.80]	0.55 [0.37, 0.83]	0.63 [0.40, 1.03]	0.51 [0.35, 0.77]	0.46 [0.30, 0.69]	1.23 [0.76, 1.93]	0.70 [0.44, 1.09]	0.68 [0.48, 0.94]		
ACQ-5 <sup>†</sup>	–		–0.28 [–0.64, 0.13]	–0.37 [–0.87, 0.14]	–0.31 [–0.80, 0.22]	–0.18 [–0.55, 0.26]	–0.34 [–0.80, 0.13]	–0.23 [–0.79, 0.34]	–0.38 [–0.97, 0.18]	–0.28 [–0.69, 0.13]		
FEV <sub>1</sub> <sup>‡</sup>	–		0.06 [–0.04, 0.16]	0.07 [–0.06, 0.20]	0.03 [–0.09, 0.14]	0.01 [–0.10, 0.11]	0.14 [0.05, 0.24]	0.10 [–0.06, 0.26]	0.13 [–0.05, 0.31]	0.09 [–0.01, 0.20]		
AE*	–		0.99 [0.62, 1.64]	1.08 [0.75, 1.59]	–	1.23 [0.62, 2.44]	1.13 [0.76, 1.65]	0.98 [0.59, 1.59]	0.94 [0.57, 1.54]	0.97 [0.68, 1.38]		
SAE*	–		2.24 [0.68, 7.29]	4.15 [1.17, 15.01]	1.42 [0.42, 4.77]	2.14 [0.77, 6.25]	0.81 [0.22, 3.03]	0.93 [0.16, 5.28]	1.55 [0.27, 8.76]	1.18 [0.32, 4.37]		
Eosinophilic												
Exacerbation rate*	–		0.54 [0.32, 0.96]	0.54 [0.31, 0.97]	0.62 [0.30, 1.3]	0.49 [0.23, 1.02]	0.46 [0.26, 0.81]	1.14 [0.52, 2.49]	0.65 [0.30, 1.42]	0.60 [0.27, 1.28]		
ACQ-5 <sup>†</sup>	–		–0.29 [–1.63, 1.08]	–0.37 [–2.14, 1.44]	–0.34 [–2.15, 1.48]	–0.27 [–2.06, 1.51]	–0.25 [–2.23, 1.76]	–0.21 [–2.12, 1.75]	–0.36 [–2.28, 1.56]	–0.23 [–2.18, 1.72]		
FEV <sub>1</sub> <sup>‡</sup>	–		0.08 [–0.22, 0.40]	0.08 [–0.32, 0.50]	0.09 [–0.33, 0.50]	0.70 [–0.34, 0.47]	0.11 [–0.20, 0.42]	0.12 [–0.33, 0.56]	0.15 [–0.30, 0.60]	0.13 [–0.32, 0.56]		
AE*	–		0.99 [0.37, 2.45]	1.07 [0.50, 2.34]	–	–	1.09 [0.53, 2.28]	–	–	–		
SAE*	–		2.12 [0.15, 29.82]	4.22 [0.35, 61.93]	1.35 [0.04, 45.97]	1.72 [0.05, 57.12]	1.35 [0.10, 19.75]	–	–	–		
Probability of being the best treatment (P <sub>i</sub> )												
Overall				Placebo	75 mg	100 mg	250 mg	750 mg	3 mg	2 mg	20 mg	100 mg
Exacerbation rate <sup>‡</sup>				< 0.01	0.08	0.13	0.03	0.22	0.51	< 0.01	0.02	0.01
ACQ-5 <sup>§</sup>				< 0.01	0.04	0.21	0.13	0.02	0.20	0.07	0.27	0.06
FEV <sub>1</sub> <sup>¶</sup>				< 0.01	0.02	0.06	0.01	< 0.01	0.37	0.15	0.33	0.05
AE <sup>‡</sup>				0.03	0.18	0.04	–	0.11	0.04	0.2	0.28	0.13
SAE <sup>‡</sup>				0.07	0.01	< 0.01	0.07	0.01	0.37	0.29	0.08	0.1
Eosinophilic												
Exacerbation rate <sup>‡</sup>				< 0.01	0.06	0.11	0.04	0.27	0.41	< 0.01	0.04	0.07
ACQ-5 <sup>§</sup>				< 0.01	0.05	0.17	0.15	0.1	0.17	0.08	0.18	0.1
FEV <sub>1</sub> <sup>¶</sup>				< 0.01	0.04	0.08	0.1	0.06	0.12	0.15	0.29	0.17
AE <sup>‡</sup>				0.3	0.43	0.14	–	–	0.14	–	–	–
SAE <sup>‡</sup>				0.26	0.06	0.06	0.25	0.17	0.23	–	–	–

\*Mean rate ratio between dose vs. placebo [95% credibility interval].

<sup>†</sup>Mean change difference vs. placebo [95% credibility interval] (expressed in L for FEV<sub>1</sub>).

<sup>‡</sup>Probability of the best reduction in the number of exacerbation rates/AE/SAE.

<sup>§</sup>Probability of the best reduction in ACQ-5 change.

<sup>¶</sup>Probability of the best increase in FEV<sub>1</sub> change.

Most of these results were expected [26, 27], but a global meta-analysis was lacking. Here, we selected significant studies and aggregated the results. This meta-analysis complied with PRISMA guidelines and fulfilled the R-AMSTAR criteria, with a total score of 41/44 (see online supplement).

We noticed some heterogeneity in the assessment of the outcome which could be attributed to 2014 Castro's studies [13]. For example, benralizumab had been tested at a very low dose and the results were nearly equivalent to those obtained for the placebo arm. We incorporated – for the sake of completeness, but at the risk of including the heterogeneity – the findings of all of the selected trials in our analysis. The relatively small number of studies including highly selected patients and the quite short drug exposure duration are other sources of concern regarding the direct transposability of these findings on a long-term basis in a real-life setting.

FDA's approval was published in November 2015 [28] regarding exacerbation rate reductions offered by the drug in 'eosinophilic asthma', especially with considerations for patients ineligible for omalizumab. Interestingly, mepolizumab was shown to be effective throughout the year, irrespective of the atopic status [29]. In the TH2 population, many patients eligible for mepolizumab may also have been eligible for omalizumab. It could potentially be expected that more dramatic IL5 blockade could have greater effects, but this was not observed with any of the three mAbs, as the highest doses never resulted in the best outcomes. The definition of eosinophilic patients was not always homogeneous across the different studies, and only five studies were thus involved in this subgroup analysis. Moreover, a single blood eosinophil threshold was used for the meta-analysis, whereas it differed in the studies. The benefits of anti-IL5 mAbs on FEV<sub>1</sub> were significant, but of moderate intensity, with a mean overall effect reaching 0.09 L in volume improvement in the overall meta-analysis, and 0.10 L in the eosinophilic subgroup. Interestingly, the level of asthma symptoms assessed via the ACQ-5 improved with anti-IL5 blockade, but only to a limited extent and usually below the MCID. It would therefore likely be difficult to identify responders.

We conducted an indirect network meta-analysis as it is unlikely that direct comparisons will ever be conducted, or only using a non-inferiority design. Only 10 trials in which multiple combinations of drugs and doses were tested could be compiled, and no reported head-to-head drug comparisons were available. Annual or annualized numbers of exacerbations were reported in most studies on the basis of a binomial negative model, or Poisson regression in others, and we opted to overlook these discrepancies. Accordingly, the rankings established in this network meta-analysis should be cautiously considered and uncertainties persisted. Our

overall feeling is that it would be nearly impossible to draw definitive conclusions on the superiority of one drug over others.

Phase III trials with benralizumab and reslizumab were not available at the moment of the study. The potential results of such trials could markedly differ from our findings, especially regarding indirect comparisons. Our results will thus require updating when phase III trial results are published. Furthermore, we did not address the issue of the oral steroid sparing effect in oral steroid-dependent patients, as the patients considered in reported studies devoted to oral steroids were pooled with the other patients.

The future will tell whether other strategies directed towards TH2 mediators are as efficient, such as IL-13 and IL-4/13 blockade. These mAbs are usually tested in milder asthma, but their potency should also be tested in severe asthma [30–32]. Promising results have been reported with non-mAbs TH2 inhibitors, and phase II studies are expected in the near future [33]. For non-eosinophilic patients, very few therapy options are currently available, or being developed, despite the fact that it represents a still unmet need in severe asthma.

In conclusion, anti-IL-5 treatment had significant effects in severe asthma patients with frequent exacerbations and evidence of eosinophilic inflammation. Reslizumab appeared to be the most effective mAb in reducing exacerbation rates and improving FEV<sub>1</sub>. Nonetheless, mepolizumab 100 mg and benralizumab 20 mg appeared to be excellent alternatives. No clear significant differences between treatments in terms of efficacy and safety were found due to the limited number of studies available.

Long-term effects, best duration of treatment and the risk of relapse after withdrawal are important issues that should be addressed in further studies. A clear definition of the satisfactory clinical response and the ideal response time for its assessment would also be warranted.

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## Conflict of interest

Pr Bourdin and Pr Chanez report advisory board membership and participation as an investigator in clinical trials sponsored by GlaxoSmithKline, Boehringer Ingelheim, Novartis, Astra Zeneca, Teva, Cephalon, Chiesi Pharmaceuticals and Sanofi.

References

1 Reddel HK, Bateman ED, Becker A *et al.* A summary of the new GINA strategy: a roadmap to asthma control. *Eur Respir J* 2015; **46**:622–39.

2 Flood-Page PT, Menzies-Gow AN, Kay AB, Robinson DS. Eosinophil's role remains uncertain as anti-interleukin-5 only partially depletes numbers in asthmatic airway. *Am J Respir Crit Care Med* 2003; **167**:199–204.

3 Bousquet J, Jeffery PK, Busse WW, Johnson M, Vignola AM. Asthma. From bronchoconstriction to airways inflammation and remodeling. *Am J Respir Crit Care Med* 2000; **161**:1720–45.

4 Bousquet J, Chanez P, Lacoste JY *et al.* Eosinophilic inflammation in asthma. *N Engl J Med* 1990; **323**:1033–9.

5 Lötvall J, Akdis CA, Bacharier LB *et al.* Asthma endotypes: a new approach to classification of disease entities within the asthma syndrome. *J Allergy Clin Immunol* 2011; **127**:355–60.

6 Wenzel SE. Asthma phenotypes: the evolution from clinical to molecular approaches. *Nat Med* 2012; **18**:716–25.

7 Rothenberg ME, Hogan SP. The eosinophil. *Annu Rev Immunol* 2006; **24**:147–74.

8 Bourdin A, Humbert M, Chanez P. Immunologic therapeutic interventions in asthma: impact on natural history. *Clin Chest Med* 2012; **33**:585–97.

9 Humbert M, Beasley R, Ayres J *et al.* Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. *Allergy* 2005; **60**:309–16.

10 Hanania NA, Wenzel S, Rosén K *et al.* Exploring the effects of omalizumab in allergic asthma: an analysis of biomarkers in the EXTRA study. *Am J Respir Crit Care Med* 2013; **187**:804–11.

11 Woodruff PG, Modrek B, Choy DF *et al.* T-helper type 2-driven inflammation defines major subphenotypes of asthma. *Am J Respir Crit Care Med* 2009; **180**:388–95.

12 Castro M, Mathur S, Hargreave F *et al.* Reslizumab for poorly controlled, eosinophilic asthma: a randomized, placebo-controlled study. *Am J Respir Crit Care Med* 2011; **184**:1125–32.

13 Castro M, Wenzel SE, Bleecker ER *et al.* Benralizumab, an anti-interleukin 5 receptor  $\alpha$  monoclonal antibody, versus placebo for uncontrolled eosinophilic asthma: a phase 2b randomised dose-ranging study. *Lancet Respir Med* 2014; **2**:879–90.

14 Lavolette M, Gossage DL, Gauvreau G *et al.* Effects of benralizumab on airway eosinophils in asthmatic patients with sputum eosinophilia. *J Allergy Clin Immunol* 2013; **132**:1086–1096.e5.

15 Castro M, Zangrilli J, Wechsler ME *et al.* Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. *Lancet Respir Med* 2015; **3**:355–66.

16 Bel EH, Wenzel SE, Thompson PJ *et al.* Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. *N Engl J Med* 2014; **371**:1189–97.

17 Ortega HG, Liu MC, Pavord ID *et al.* Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med* 2014; **371**:1198–207.

18 Pavord ID, Korn S, Howarth P *et al.* Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet* 2012; **380**:651–9.

19 Flood-Page P, Swenson C, Faierman I *et al.* A study to evaluate safety and efficacy of mepolizumab in patients with moderate persistent asthma. *Am J Respir Crit Care Med* 2007; **176**:1062–71.

20 Haldar P, Brightling CE, Hargadon B *et al.* Mepolizumab and exacerbations of refractory eosinophilic asthma. *N Engl J Med* 2009; **360**:973–84.

21 Cochrane Handbook for Systematic Reviews of Interventions [Internet]. Disponible sur: <http://handbook.cochrane.org/> [cité 6 oct 2016].

22 Dias S, Welton NJ, Sutton AJ, Ades AE. *NICE DSU Technical Support Document 2: a generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials*. London, UK:National Institute for Health and Care Excellence (NICE)

23 Jansen JP, Fleurence R, Devine B *et al.* Interpreting indirect treatment comparisons and network meta-analysis for health-care decision making: report of the ISPOR task force on indirect treatment comparisons good research practices: Part 1. *Value Health* 2011; **14**:417–28.

24 Lunn D, Spiegelhalter D, Thomas A, Best N. The BUGS project: evolution, critique and future directions. *Stat Med* 2009; **28**:3049–67.

25 Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. *Eur Respir J* 1999; **14**:902–7.

26 Liu Y, Zhang S, Li D, Jiang S. Efficacy of anti-interleukin-5 therapy with mepolizumab in patients with asthma: a meta-analysis of randomized placebo-controlled trials. *PLoS ONE* 2013; **8**:e59872.

27 Powell C, Milan SJ, Dwan K, Bax L, Walters N. Mepolizumab versus placebo for asthma. *Cochrane Database Syst Rev* 2015; **7**:CD010834.

28 Keating GM. Mepolizumab: first global approval. *Drugs* 2015; **75**:2163–9.

29 Ortega H, Chupp G, Bardin P *et al.* The role of mepolizumab in atopic and nonatopic severe asthma with persistent eosinophilia. *Eur Respir J* 2014; **44**:239–41.

30 Corren J, Lemanske RF, Hanania NA *et al.* Lebrikizumab treatment in adults with asthma. *N Engl J Med* 2011; **365**:1088–98.

31 Wenzel S, Ford L, Pearlman D *et al.* Dupilumab in persistent asthma with elevated eosinophil levels. *N Engl J Med* 2013; **368**:2455–66.

32 Gauvreau GM, O'Byrne PM, Boulet L-P *et al.* Effects of an anti-TSLP antibody on allergen-induced asthmatic responses. *N Engl J Med* 2014; **370**:2102–10.

33 Krug N, Hohlfeld JM, Kirsten A-M *et al.* Allergen-induced asthmatic responses modified by a GATA3-specific DNase. *N Engl J Med* 2015; **372**:1987–95.