EUROPEAN RESPIRATORY journal

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Task Force Report

Management of Severe Asthma: a European Respiratory Society/American Thoracic Society Guideline

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Please cite this article as: Holguin F, Cardet JC, Chung KF, *et al*. Management of Severe Asthma: a European Respiratory Society/American Thoracic Society Guideline. *Eur Respir J* 2019; in press (https://doi.org/10.1183/13993003.00588-2019).

Management of Severe Asthma: a European Respiratory Society/American Thoracic Society Guideline.

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Abstract:

This document provides clinical recommendations for the management of severe asthma. Comprehensive evidence syntheses, including meta-analyses, were performed to summarise all available evidence relevant to the Task Force's questions. The evidence was appraised using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach and the results were summarized in evidence profiles. The evidence syntheses were discussed and recommendations formulated by a multidisciplinary Task Force of asthma experts, who made specific recommendations on 6 specific questions. After considering the balance of desirable and undesirable consequences, quality of evidence, feasibility, and acceptability of various interventions, the Task Force made the following recommendations: 1) Suggest using anti-IL5 and anti IL-5Rα for severe uncontrolled adult eosinophilic asthma phenotypes; 2) suggest using blood eosinophil cut-point of ≥ 150/μl to guide anti-IL5 initiation in adult patients with severe asthma; and 3) Suggest considering specific eosinophil (≥ 260 /μl) and FeNO (≥19.5 ppb) cutoffs to identify adolescents or adults with the greatest likelihood or response to anti-IgE therapy; 4) Suggest using inhaled tiotropium for adolescents and adults with severe uncontrolled asthma despite GINA step 4-5 or NAEPP step 5 therapies; 5) Suggest a trial of chronic macrolide therapy to reduce asthma exacerbations in persistently symptomatic or uncontrolled patients on GINA step 5 or NAEPP step 5 therapies, irrespective of asthma phenotype ; 6) Suggest using anti-IL4/13 for adult patients with severe eosinophilic asthma, and for those with severe corticosteroid-dependent asthma regardless of blood eosinophil levels. These recommendations should be reconsidered as new evidence becomes available.

Introduction

The first European Respiratory Society (ERS) - American Thoracic Society (ATS) guidelines on severe asthma in adults and school age children were published in 2014 (1). Severe asthma was defined as follows: 'When the diagnosis of asthma is confirmed and comorbidities addressed, severe asthma is defined as asthma that requires treatment with high dose inhaled corticosteroids plus a second controller and/or systemic corticosteroids to prevent it from becoming ''uncontrolled'' or that remains ''uncontrolled'' despite this therapy'. Emphasis was placed on the necessity to confirm the diagnosis of asthma and exclude other conditions that may mimic asthma. In addition, the guidelines recognised that severe asthma is a heterogeneous condition consisting of phenotypes such as severe eosinophilic asthma and specific recommendations were made on the use of sputum eosinophil count and exhaled nitric oxide to guide therapy. Recommendations were also made for the use of methotrexate, macrolide antibiotics, antifungal agents, bronchial thermoplasty and the anti-IgE antibody (omalizumab) in severe asthma.

This current guideline, for which work commenced in 2017, is also an ERS-ATS collaboration and was initiated in view of the rapid introduction of new treatments for severe asthma, particularly the new biologic treatments approved for the management of severe eosinophilic asthma. Six specific and important questions were formulated using the Patient population, Intervention, Comparison and

Outcome (PICO) format. The GRADE approach was used to assess the strength of evidence and develop recommendations (2)

The six questions chosen and developed by the Task Force are shown in Table 1:

Table 1. ERS/ATS Severe Asthma Task Force Questions
1. Should a monoclonal anti-IL5 antibody be used in adults and children (for the purposes of this guideline, age >5 years) with severe asthma?
2. Should a measurement of a specific biomarker be used to guide initiation of treatment with a monoclonal anti-IL5 antibody or anti-ILR∝ in adults and children with severe asthma? (chosen biomarkers being exhaled NO, peripheral or sputum eosinophils, and serum periostin)
3. Should a measurement of a specific biomarker be used, in addition to total IgE level, to guide initiation of treatment with a monoclonal anti-IgE antibody in adults and children with severe asthma? (chosen biomarkers being exhaled NO, peripheral or sputum eosinophils, and serum periostin)
4. Should a long-acting inhaled muscarinic antagonist (LAMA) be used in adults and children with severe asthma?
5. Should a macrolide (i.e., azithromycin, clarithromycin) be used in adults and children with severe asthma?
6. Should a monoclonal anti-IL4Rα be used in adults and children with severe asthma?

During the deliberations of the Task Force, it became clear that the IL4Rα blocker, which modulates the effects of IL4 and IL13 would receive approval by the regulatory authorities, so the 6th PICO was instituted, having originally not been considered. The Task Force was focused on these specific PICOs, and, unlike the first Task Force, did not consider general management strategies for severe asthma.

Methods

A detailed description of the methodology used to develop the questions, rate the outcomes, select the studies, and synthesising, formulating and grading the evidence is available in previous ERS/ATS guidelines and in the on-line supplement(3, 4).

Group composition

The ERS and ATS selected the Task Force co-chairs (F.H, A.B), who led the project and selected the other panelists, which included 23 clinicians and researchers with experience in severe asthma and two severe asthma patient representatives (B.F, D.H). Two methodologists (D.R, R.M), lead by the ERS senior methodologist (T.T), supervised and ensured that all the methodological requirements were met. Systematic reviews and application of the GRADE approach were performed by members of the TF (DF, SD) and externally commissioned (Iberoamerican Cochrane Centre). The methodologist took part in the Task Force meetings but did not participate in the formulation of recommendations and had no voting rights.

The co-chairs and panelists discussed the evidence and formulated the recommendations. Evidence profiles and Evidence to Decision (EtD) tables (See supplement) developed with the GRADEpro Guideline Development Tool (McMaster University, 2015; available from gradepro.org.) were used to facilitate the discussions, which was followed by voting on the recommendations. All panel members disclosed their conflicts of interest. Both co-chairs were required to be free from conflicts of interest relating to the management of asthma. Individuals with relevant conflicts of interest (COI) took part in the discussions about the evidence but did not participate in the formulation of recommendations related to the questions where they had a relevant COI.

Thresholds for clinically important differences between treatment groups primarily in adults (used to judge imprecision according to GRADE) included the following absolute reductions: St George's Respiratory Questionnaire (SGRQ) score change of 4 units, Asthma Control Questionnaire (ACQ-5, ACQ-6, and ACQ-7) score change of 0.5 units, Asthma Quality of Life Questionnaire (AQLQ) score change of 0.5 units, Forced Expiratory Volume in one second (FEV_1) change in Liters 0.23 and change in percentage 10.38%%(5-7).

Literature searches

The librarians (S.K, L. K) conducted the literature search strategies in Medline In-Process & Other Non-Indexed Citations, MEDLINE, Embase, and Cochrane Central Register of Controlled Trials (CCTR), beginning in 2008 and ending with a final update on 27 September 2018. These dates were selected to capture developments in severe asthma therapy since the previous ERS/ATS guidelines. The literature searches included systematic reviews of randomised clinical trials including (moderate to severe) asthma population receiving the interventions of interest. We excluded: Phase I (pharmacokinetic or pharmacodynamic studies), real-life non-randomised extension studies, and research reported in abstract form only such as poster or congress presentations.

Results were limited to human subjects and to reports in the English language. Each strategy incorporated medical subject headings and text words for the topic of asthma, with search hedges for specific concepts defined in the PICOs. To

supplement the electronic search, contacted experts were contacted journals and reference lists were hand-searched.

Evidence Synthesis.

Study characteristics, types of participants, interventions, outcome measures and results were extracted from each study. If the data were amenable to pooling, effects were estimated by meta-analysis using Review Manager (version 5.3; The Nordic Cochrane Centre, Copenhagen, Denmark). For the meta-analyses, the random effects model was utilised unless otherwise specified. Dichotomous outcomes were reported as relative risks and continuous outcomes were reported as mean differences unless otherwise specified. Absolute differences are reported in the accompanying documents in the appendix. Judgements on the quality of evidence were reviewed by the TF members and validated by the ERS Methodologists (TT, DR, RM).

Formulating and grading recommendation

The evidence profiles were sent to the Task Force members for review. Using an iterative consensus process conducted face-to-face and also via teleconference and via email, and finally a vote by all members of the Task Force who had no relevant conflicts, recommendations were formulated on the basis of the following considerations: the balance of desirable (benefits) and undesirable consequences (burden, adverse effects and cost) of the intervention, the quality of evidence,

patient values and preferences, and feasibility [10]. A strong recommendation was made for or against an intervention when the panel was certain that the desirable consequences outweighed the undesirable consequences (or the converse for recommendation against). A strong recommendation is one that most well informed patients would follow.

A conditional recommendation was made for or against an intervention when the panel was uncertain that the desirable consequences of the intervention outweighed the undesirable consequences (or the converse, for recommendation against). Reasons for uncertainty included low or very low quality of evidence, the desirable and undesirable consequences being finely balanced, the population in reviewed studies not uniformly meeting ERS/ATS severe asthma criteria, or the underlying values and preferences playing an important role. A conditional recommendation indicates that well-informed patients may make different choices regarding whether to have or not have the intervention.

Manuscript preparation

The two co-chairs, ERS methodologists and one panelist (KFC) developed the initial manuscript draft. The ERS methodologists and PICO leaders prepared the EtD tables in the supplementary material. All materials were edited and approved by all panel members.

Supporting documentation, including GRADE Evidence profiles and the Evidence to Decision Frameworks tables is included in the online supplement.

Results:

Should a monoclonal anti-IL5 antibody be used in adults and children with severe asthma?

Interleukin 5 (IL-5) is a principal cytokine driving eosinophilic inflammation in asthma. Monoclonal antibodies that target IL-5 (mepolizumab, reslizumab) or its receptor IL-5Rα (benralizumab) have been found to be efficacious in randomized controlled trials (RCTs) in improving asthma-related outcomes, and are currently approved by the U.S. Federal Drug Administration (FDA)/European Medicines Agency (EMA). We identified 12 RCTs that met inclusion criteria. We included data only for participants on FDA/EMA licensed doses or the 20 mg SC dose from phase 2 benralizumab trials. The evidence from meta-analyses of these trials is summarized below. Asthma exacerbations, symptoms, asthma control, quality of life, use of systemic corticosteroids and adverse events were considered 'critical outcomes". Change in lung function was deemed an 'important' outcome.

Summary of the evidence

Mepolizumab:

Three studies in adolescents and adults met inclusion criteria (8-10). All three were randomized placebo-controlled trials in patients with severe eosinophilic asthma (blood eosinophil count $\geq$ 300 cells/mm^3 in the 12 months prior to screening or $\geq$ 150 cells/mm^3 during screening/oral corticosteroid [OCS] optimization period) considered by this Task Force to represent a population of severe asthmatics as

defined by the ERS/ATS Guidelines on Severe Asthma. Two studies required patients to have had at least two attacks in the previous year despite regular use of high dose inhaled corticosteroid (ICS) plus another controller (9, 10), whereas the other investigated the steroid-sparing effect of mepolizumab in OCS-dependent asthma (8).

Mepolizumab therapy was associated with a 50% reduction in the rate of any exacerbation (rate ratio 0.5; 95%CI 0.39, 0.65; absolute risk 0.92 versus 1.69 events/patient/year) and 64% reduction in exacerbations requiring emergency department (ED) visit or hospitalization (rate ratio 0.36; 95% CI 0.20, 0.66; 0.05 versus 0.15 events/patient/year). Compared to placebo, those assigned to mepolizumab experienced an absolute 0.43-point decrease (i.e. improvement) in ACQ-5 (95% CI -0.56, -0.31); and an absolute 7.14 decrease (i.e. improvement) in the SGRQ scale (95% CI -9.07, -5.21). Mepolizumab, relative to placebo, resulted in a 50% median reduction in the dose of maintenance oral corticosteroids (OCS) (95% CI 20, 75) in one study of 135 patients(8). The effect of mepolizumab on FEV_1 was less than the minimal clinically important difference (MCID) threshold.

Reslizumab:

Four publications that included five RCTs met the inclusion criteria (11-14). Castro et al, 2015 reported on two duplicate trials (13). Three of the five RCTs included adolescents in addition to adult participants (11, 13). All studies except one (12) included patients with mixed severity (moderate and severe) asthma. Three RCTs used inclusion criteria of blood eosinophils $\geq$ 400 cells/mm^3 (11, 13, 14) and one

RCT used sputum eosinophil ≥ 3% (12). One RCT included participants unselected for blood eosinophil count but subsequently performed a subgroup analysis using a blood eosinophil cutoff of 400 cells/mm^3 (14). Overall, reslizumab therapy was associated with a 54% reduction in any exacerbation (rate ratio 0.46; 95%CI 0.37, 0.58; 0.84 versus 1.81 events/patient/year) relative to placebo and 33% reduction in exacerbations requiring ED visits or hospitalizations (rate ratio 0.67; 95% CI 0.39, 1.17; 0.077 versus 0.12 events/patient/year). Reslizumab therapy also reduced the risk of patients having at least one exacerbation (29.2% versus 46.7%; risk ratio [RR] 0.63; 95%CI 0.53, 0.76). In a study of participants meeting the ATS/ERS criteria for diagnosis of severe asthma , reslizumab therapy was associated with a 60% reduction in the risk of having ≥ 1 exacerbation (7.5% versus 18.9%; RR 0.40; 95% CI 0.13, 1.20)

Relative to participants on placebo, those assigned to reslizumab experienced an absolute 0.26-point decrease (i.e. improvement) in ACQ-7 (95% CI -0.33, -0.18); and an absolute 0.28-point increase (i.e. improvement) in AQLQ scale (95% CI 0.17,0.39). The effect of reslizumab on FEV_1 did not cross the MCID threshold.

Benralizumab:

Five RCTs evaluating benralizumab met the inclusion criteria(15-19). Four studies included a mixed population of patients with moderate or severe asthma (15-18). Two of the five RCTs included adolescents in addition to adult participants (15, 17). One study investigated the steroid-sparing effect of benralizumab in OCS-dependent asthma (18)

Overall, benralizumab therapy was associated with a 42% reduction in the rate of any exacerbation (rate ratio 0.58; 95%CI 0.47, 0.73; 0.64 versus 1.19 events/patient/year) and a 38% reduction in the number of patients with ≥1 exacerbation (35.9% versus 51.1%; RR 0.62; 95%CI 0.36, 1.06) relative to placebo. In study participants meeting ATS/ERS criteria for diagnosis of severe asthma, benralizumab therapy was associated with 55% reduction in exacerbations (number of patients with ≥1 exacerbation 23.3% versus 52%; RR 0.45; 95% CI 0.28, 0.72). Those requiring ED visits or hospitalizations were also reduced (rate ratio 0.45; 95% CI 0.14, 1.47; 0.043 versus 0.18 events/patient/year), and with a greater magnitude for patients meeting ATS/ERS criteria for diagnosis of severe asthma (rate ratio 0.07; 95% CI 0.01, 0.63; 0.02 versus 0.32 events/patient/year) Relative to participants on placebo, those assigned to benralizumab experienced an absolute 0.29-point decrease in ACQ-6 (95% CI -0.4, -0.17); and an absolute 0.32-point increase (i.e. improvement) in AQLQ scale (95% CI 0.19, 0.45). The effect of benralizumab on FEV_1 was below the MCID. The median OCS dose reduction from baseline (range) at the final visit (week 28) was 25.0% (−150% to 100%) in the placebo group (n=75) and 75.0% (−50% to 100%) in the benralizumab group (n=73) (18).

Adverse effects:

Compared to placebo, the risk ratio of developing any adverse event for a participant was 0.93 (95% CI 0.88, 0.99) for mepolizumab (74.8% versus 79.6%); 0.88 (95% CI 0.81, 0.96) for reslizumab (67.1% versus 80.4%), and 0.96 (95% CI

0.91 – 1.01) for benralizumab (73.6% versus 75.5%). Similarly, participants experienced a lower risk of serious adverse events when assigned to anti-IL5 strategy drugs (see on-line supplement). The lower risk for having any adverse events is likely driven by the reduction in severe asthma exacerbations by these drugs.

Data are available on *drug-related* adverse events from all 3 mepolizumab trials, but only from 2 of 5 reslizumab trials and 1 of 5 benralizumab trials. These data show that, relative to placebo, participants assigned to mepolizumab had a greater risk of drug-related adverse events (13.3% versus 9.2%; RR 1.35, 95%CI 1.01, 1.80); those assigned to reslizumab had a lower risk (8% versus 11.9%; RR 0.69; 95%CI 0.44, 1.09) and those assigned to benralizumab had a greater risk (13.3% versus 9.2%; RR 1.46; 95%CI 0.96, 2.21). Because the outcome drug-related adverse events were not pre-defined, the TF members did not consider this outcome in the overall certainty of the evidence of effects.

Benefits

Anti-IL5 and anti-IL5Rα therapies reduce exacerbations and hospitalizations in patients with severe eosinophilic asthma. Mepolizumab and benralizumab are effective in reducing maintenance OCS dose in patients with corticosteroid-dependent severe asthma.

Harms

All three anti-IL5 strategy drugs were well tolerated. Frequency of adverse effects was similar when compared with placebo.

Conclusions

Anti-IL5 strategy reduces exacerbations in patients with severe eosinophilic asthma. Mepolizumab and benralizumab are effective in reducing OCS dose in corticosteroid-dependent asthma. The effects on asthma control, quality of life and FEV_1 are modest for all drugs and did not meet the MCID threshold.

Research needs and additional considerations

Direct comparisons will be needed to further guide selection of the appropriate anti-IL5 drug. Uncertainty exists around the best biomarker and blood eosinophil threshold that would predict response to anti-IL5 therapy. In addition to blood eosinophils, the efficacy of anti-IL5 therapy depends on the degree of preexisting asthma exacerbations. This should be taken into consideration when considering the clinical and cost effectiveness of this form of therapy. Data from adolescents are unavailable for mepolizumab and reslizumab, whereas for benralizumab, there are data on a limited number of adolescents with severe asthma. There are no data on younger children. Therefore, more evidence is needed to provide greater quality recommendations in the pediatric age group.

What others are saying

Global Initiative for Asthma (GINA) (20) and the National Institute for Health and Care Excellence (NICE)(21) technology appraisal guidance TA431, TA479 and TA565 include mepolizumab, reslizumab and benralizumab as add-on therapeutic option for severe eosinophilic asthma (at Step 5 of GINA).

ERS/ATS recommendation

We suggest anti-IL5 strategy as add-on therapy for adult patients with severe uncontrolled asthma with an eosinophilic phenotype (The task force gave this a conditional recommendation because inclusion criteria across studies did not consistently aligned with the ERS/ATS severe asthma definition).

Remarks: The high cost of these drugs and its impact on cost effectiveness, equity and feasibility to implementation must be weighed by clinicians in relation to the benefits on asthma outcomes shown by all anti-IL5 and anti-IL5Ra strategy drugs(22). Due to limited number of treated adolescents or children, the TF was unable to provide a recommendation for the use of anti-IL5 and anti-IL5Ra antibodies in this age group.

Should a measurement of a specific biomarker be used to guide initiation of treatment with a monoclonal anti-IL5 or IL5Rα antibody in adults and children with severe asthma? (biomarkers being exhaled NO, peripheral or sputum eosinophils, and serum periostin)

Summary of the evidence

We identified 12 randomized controlled trials of anti-IL5 therapies in children and adults 12-75 years of age that evaluated differential response to therapy amongst

subgroups of individuals with higher or lower levels of eosinophils in blood or sputum in *post hoc* analyses (10-17, 19, 23, 24). One paper was a meta-analysis of 2 RCTs of mepolizumab's therapeutic responsiveness combining the 100 mg SC and 75 mg IV doses for the analysis by blood eosinophil level (24). Notably, four of the studies recruited only subjects with evidence of eosinophilic asthma, defined as a sputum eosinophil of ≥3% or blood eosinophil level of ≥300/uL (11-13, 23). Six of the studies included children ≥ 12 years (10, 11, 13, 15, 17, 24). The most commonly measured biomarker was blood eosinophil count. Only one study evaluated sputum eosinophil level (12). One additional study evaluated whether the presence of persistently elevated sputum or blood eosinophils was an indicator of therapeutic failure and justified the addition of an alternate anti-IL5 strategy (25).

Cut-offs assessed for baseline blood eosinophil levels, and hence the definition of what constitutes eosinophilia, varied across anti-IL5 strategies. Studies of mepolizumab specifically assessed a cut-off of blood eosinophils of ≥150/uL. For mepolizumab, there was a 73% (95%CI -82, -59%) reduction in exacerbations amongst those with a blood eosinophil level of ≥ 500/uL compared to 36-39% reduction in all other groups with eosinophil levels ≥ 150/uL. Notably, subjects with eosinophil levels of ≥150/uL constituted nearly three quarters of the severe asthma population in those studies. Patients treated with reslizumab with a baseline eosinophil of ≥400/uL had a 54% reduction in exacerbations; higher cut-offs were not associated with a greater reduction in exacerbations. For benralizumab, a cut-off of ≥300/uL was associated with a significant reduction in

exacerbations; however, it is not clear what the optimal cut-off should be since even subjects with an eosinophil level of <300/uL experienced a reduction in exacerbations.

For effects on asthma control and quality of life, the data again varied by anti-IL5 strategy; among those with a baseline eosinophil level of ≥150/uL, 63% treated with mepolizumab vs 41% treated with placebo, achieved a ≥ 0.5-point reduction from baseline in ACQ-5 (RR 1.53, 95%CI 1.27 – 1.84). The improvement in asthma control was similar among those with higher baseline levels of eosinophils (≥300 or ≥500). For benralizumab, only subjects with a baseline eosinophil level of ≥300/uL experienced a significant improvement in asthma control, assessed as change in ACQ-6 score from baseline (mean difference -0.28 [95%CI -0.41, - 0.15]); whereas those with an eosinophil level of <300/uL did not (-0.20 [95%CI -0.44, 0.3]). Similarly for reslizumab, a cut-off of ≥ 400/uL was associated with improved asthma control (mean difference in ACQ-7) from baseline -0.27 (95%CI -0.36, -0.19); whereas those below 400/uL did not have a significant benefit (-0.12 [95%CI -0.33, 0.09]). Sputum eosinophil level was only considered in one study of reslizumab (12) and sputum levels were categorized as ≥ or < 10%. There were no statistical differences found between groups in level of asthma control. There was a trend for higher blood eosinophil levels to be associated with a greater improvement in asthma control.

One additional study, which was not included in the meta-analysis, assessed treatment response of weight-adjusted IV reslizumab in patients previously treated

with 100-mg SC mepolizumab (25). It reported that persistently high levels of eosinophils (blood >300/uL and sputum >3%) after treatment with mepolizumab characterized responders. In those subjects a weight-adjusted dose of reslizumab was administered. It was found that further improvements in symptoms and reductions in eosinophilia were possible with addition of Reslizumab. These data suggest that evidence of uncontrolled eosinophilic inflammation, as manifested by a high sputum or blood eosinophil level, may be useful in determining which subjects may benefit from additional anti-IL5 strategies; however, this need further requires confirmation.

Benefits

The specific cut-off blood eosinophil count to predict improved asthma control and reduction in exacerbations varies across anti-IL5 strategies. However, there is very low quality evidence that mepolizumab may provide further benefit in reducing exacerbations in patients with baseline blood eosinophilia ≥ 500/µL compared to those with an eosinophil level <150/µL, 150 to < 300/µL and 300 to <500/µL.

Harms

There were 5 papers that assessed adverse events in benralizumab or reslizumab (11, 13-17). The data for mepolizumab did not assess differences in adverse event rates based on blood eosinophil level. There was no difference in adverse events amongst those with higher vs lower eosinophil counts for benralizumab. For Reslizumab, only subjects with a baseline eosinophilia of >400/uL during screening

were recruited; the fewest adverse events occurred in the group who had no data on eosinophil count at the time of recruitment compared to patients with baseline eosinophilia ≥400/uL. There was a 5% reduction in the number of adverse events amongst those with an eosinophil count of ≥400/uL which, although statistically relevant, may not be clinically meaningful. More recent studies have now shown that both benralizumab and mepolizumab, maintain an adequate safety profile during long term use for up to 2 and 4.5 years, respectively (26, 27).

Other considerations

Most of the studies focused on blood eosinophils as a biomarker and there was limited data on sputum eosinophils and no data on FeNO or serum periostin. Blood eosinophils can be measured in any standard laboratory increasing its feasibility as a biomarker, yet additional testing beyond the point of care maybe required to ascertain baseline levels, particularly among patients on or recently taking systemic corticosteroids. It is more acceptable than sputum eosinophil levels, which are currently only performed in specialized centers. It should be noted that there may be causes other than atopy (e.g. parasitic infections) for peripheral blood eosinophilia specially in low and middle-income settings.

Cut-offs to assess response varied across studies of anti-IL5 medications and there was no data comparing therapeutic regimens using different cut-off levels. Finally, most of the anti-IL5 strategies use a fixed dose regimen based on RCT data suggesting a plateau in the dose response; however, one study suggested that

persistent eosinophilia, despite anti-IL5 strategies, should be considered as an opportunity to add on reslizumab using a weight-adjusted dose regimen(25).

Conclusions and research needs:

Although the data suggest that subjects with higher levels of blood eosinophil counts benefit more from anti-IL5 strategies, the evidence we reviewed does not show that a specific level of blood eosinophils greater than or equal to 150/μL for mepolizumab, ≥300/μL for benralizumab and ≥400/μL for reslizumab is an absolute response threshold, as clinical benefit can still be observed in some patients below these values. Based on currently available evidence (which is very limited) sputum eosinophils may not add to the prediction of response greater than blood eosinophil level.

Determining a patient's baseline eosinophil count may require more than one measurement, as this biomarker is highly variable and significantly reduced by systemic and inhaled corticosteroids. It is not known if eosinophil levels obtained during periods of asthma exacerbation are better predictors of treatment response when compared to those measured during periods of clinical stability. Future studies should focus on developing additional non-invasive biomarkers for adults and children that can be used at point-of-care to predict responsiveness to different anti-IL5 strategies.

What others are saying:

GINA 2018 guideline for difficult to treat and severe asthma recommends the use of an anti-IL5 and anti-IL5Ra strategy for patients who are continuing to experience severe exacerbations despite step 4 or 5 therapy who have blood eosinophils ≥ 300/μL.

ERS/ATS recommendation:

We suggest that a blood eosinophil count cut-off point of ≥ 150 /μL can be used to guide anti-IL5 initiation in adult patients with severe asthma and a history of prior asthma exacerbations (conditional recommendation, low quality evidence).

Remarks

The TF placed a high value on reducing exacerbations and a greater feasibility of biomarker measurement and a lower value on cost and invasiveness.

Should a measurement of a specific biomarker be used, in addition to total IgE level, to guide initiation of treatment with a monoclonal anti-IgE antibody in adults and children with severe asthma? (biomarkers being exhaled NO, peripheral or sputum eosinophils, and serum periostin)

Summary of the evidence

We identified three randomised, double blind placebo-controlled trials(28-30) which recruited participants aged 12-75 years. Of these, two studies(29, 30) involving 1014 eligible participants formed the evidence for the taskforce recommendation. These two trials included individuals with uncontrolled asthma; in one of them (30), patients had uncontrolled symptoms whilst taking an inhaled corticosteroid (ICS) with or without a controller. In the other study (29), only

participants with severe persistent asthma were recruited, whose asthma remained uncontrolled despite ICS and a long acting beta2 agonist.

In both trials eligible participants were randomised 1:1 to receive omalizumab or placebo. Omalizumab dose was determined on the basis of pretreatment serum total IgE level (IU/mL) and body weight (kg) according to the European (30) or ATS (29) omalizumab dosing table, which ensured a minimum omalizumab dose of 0.008 mg/kg/IgE (IU/mL) every 2 weeks or a minimum of 0.016 mg/kg/IgE (IU/mL) every 4 weeks.

Busse et al.(30) preplanned an analysis that divided participants into two subgroups according to eosinophil counts at screening; low (<300/µl) and high (≥300/µl). A subgroup analysis was performed by Hanania(29), which divided participants into high and low subgroups as follows: FeNO - low<19.5 ppb, high ≥19.5 ppb; peripheral blood eosinophils - low<260/µl and high ≥260/µl and serum periostin levels – low <50 ng/ml and high ≥50 ng/ml.

Pooling of the data from the two studies was not possible. In Busse et al (30) there were significant improvements in exacerbation rates (hazard ratio [HR] 0.41 [95%CI 0.20, 0.84]) and a clinically trivial but statistically significantly greater change in FEV_1 %predicted at 24 weeks (mean difference [MD] 7.35 ml [95%CI 1.38, 13.32]) with omalizumab compared to placebo in patients with a high eosinophil count, whereas there were no differences in patients with low eosinophils (less than

300/uL). In the study by Hanania(29) there was a significantly longer time to first asthma exacerbation with omalizumab compared to placebo in patients with high (260/uL or more) eosinophil count at 48 weeks follow-up (HR 0.64 [95%CI 0.48. 0.85]), whereas there were no differences in patients with low (less than 260/uL) eosinophil count (HR 0.95 [95%CI 0.68, 1.33]). However, there were no statistically significant differences between these subgroups. There were no differences in AQLQ at 48 weeks, when omalizumab was compared to placebo in patients with high eosinophils (260/uL or more) (MD 0.14 [95%CI -0.11, 0.30]), while there was a small statistically, but not clinically significant, difference in the low eosinophil subgroup (MD 0.26 [95%CI 0.06, 0.46]).

In the subgroup analysis by FeNO (29), there was a significant relative reduction of exacerbation rates with omalizumab compared to placebo in patients with high (19.5 ppb or more) FeNO level at 48 weeks follow-up (53% [95% Cl 37-70]), whereas there were no differences for those patients with low (less than 19.5 ppb) FENO levels (16% [95% CI: -32 to 46]). The time to first asthma exacerbation with omalizumab, compared to placebo, was significantly longer in patients with high (19.5 ppb or more) FeNO level at 48 weeks follow-up (HR 0.38 [95%CI 0.24, 0.60]), whereas there were no differences in patients with low (less than 19.5 ppb) FeNO (HR 1.00 [95%CI 0.62, 1.61]). There were also larger changes of mean AQLQ with omalizumab compared to placebo in FeNO high patients (19.5 ppb or more) at 48 weeks of follow-up (MD 0.39 [95%CI 0.06, 0.72]), whereas there were no differences in FeNO low patients (less than 19.5 ppb) (MD 0.24 [95%CI -0.09, 0.57]).

There were no differences in the relative reduction of exacerbation rates at 48 weeks or FEV1 when omalizumab was compared to placebo in periostin high (50 ng/ml or more) or low (less than 50 ng/ml) patients(29). However, compared to placebo, omalizumab improved AQLQ in patients with low (less than 50 mg/ml) periostin levels at 48 weeks follow-up (MD 0.50 [0.22,0.78]), whereas there were no differences patients with high (50 ng/ml and more) serum periostin levels (MD 0.10 [95%CI -0.19,0.39]).

Benefits

In patients treated with omalizumab compared to placebo, the presence of a baseline blood eosinophil count of greater or equal to 260/µl is associated with greater improvements in FEV_1, and a decreased rate of exacerbations as well as longer time to first exacerbation, compared to those with a blood eosinophil count less than 260/µl.

In patients treated with omalizumab compared to placebo, the presence of FeNO level of greater or equal 19.5 ppb is associated with improvements in AQLQ, reduced exacerbation rate and longer time to first exacerbation, compared to those with a FeNO level less than 19.5 ppb. In patients treated with omalizumab compared to placebo, the presence of a periostin level less than 50ng/ml was associated with improvements in AQLQ, compared to those with a periostin level greater than or equal to 50ng/ml. Periostin levels, however, did not predict

response in exacerbations or lung function. There is no evidence that periostin is a suitable biomarker to guide asthma treatment in children or adolescents. Levels are influenced by age, skeletal growth and puberty (31).

Harms

There were no differences in the adverse effects in patients treated with omalizumab versus placebo according to high or low FeNO, blood eosinophils or periostin.

Other considerations

The estimates of effect included one single study (meta-analysis of the two RCT was not possible), which introduced some uncertainty due to the limited number of patients included in each subgroup according to biomarker's threshold..
Furthermore, the risk of bias was high for completeness of data, due to a considerable number of patients that were not evaluated at baseline for the biomarkers.

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Conclusions and research needs

Blood eosinophil counts and FeNO levels may be useful in choosing patients most likely to achieve a more positive effect on exacerbations and lung function when treated with omalizumab compared to placebo. There were no differences in adverse effects based on the biomarker high and low subgroups, suggesting that the

blood eosinophil- and FeNO-high patients achieve clinical benefit without additional adverse effects, whereas, biomarker low patients are at risk of adverse effects while potentially having less clinical benefit.

Other excluded studies also make important observations regarding the use of blood eosinophil to select patients most likely to respond to omalizumab. Of particular note is the study by Casale et al., who reported an analysis that pooled the results of two RCTs (32). The studies by Busse et al (33) and Soler et al (34) were both phase III, double blind placebo controlled trials, comprising a total of 1071 participants comparing omalizumab to placebo in participants with moderate to severe asthma. The pooled analysis published in 2018 investigated the annualized exacerbation rates in the omalizumab group versus placebo according to the subgroups of blood eosinophil high (≥300/μl) and low (<300/μl)(32). The results support the recommendations of the taskforce. There was a more pronounced reduction in exacerbations rates in the omalizumab versus placebo group for the biomarker high subgroup; i.e., for those with an eosinophil count ≥300/μl there was a 67% reduction in exacerbations, in contrast to a 45% reduction in the < 300/μl group.

In contrast to the previous studies, one publication found that omalizumab's effectiveness did not vary across biomarker levels. This retrospective study of 872 patients with severe allergic asthma showed that omalizumab reduced exacerbations by 58.4% (95% CI 52.7, 63.4%) in the biomarker high (eosinophil

count ≥300/μl) group, vs. 58.1% (95% CI 52.7, 63.4%) in the biomarker low group (eosinophil count <300/μl)(35).

Future randomised controlled trials should evaluate baseline blood eosinophils and FeNO as individual and combined biomarkers to further determine their ability to predict response to treatment for multiple outcomes including exacerbations, lung function as well as patient reported outcomes such as AQLQ and asthma control. Furthermore, there is a need to identify biomarkers that support clinical decision-making regarding the continuation versus discontinuation of a monoclonal anti-IgE strategy in adults and children with severe asthma.

What others are saying

The 2018 GINA guidelines for the Diagnosis and Management of Severe Asthma in adolescent and adult patients state that a blood eosinophil level of ≥260/μl and FeNO ≥20 ppb are factors that may predict a good response to treatment.
Neither the British Thoracic Society nor the NICE asthma guidelines make comment about predictor biomarkers foranti-IgE treatment response.

ATS/ERS recommendation

In adult and adolescent patients with severe asthma being considered for omalizumab we suggest:

- Using a blood eosinophil cut-off of ≥ 260 /μl to identify adolescents (>12 years) and adults with severe allergic asthma more likely to

benefit from anti-IgE treatment (conditional recommendation, low quality of evidence).

- Using a FeNO cut-off of ≥ 19.5 ppb to identify adolescents (>12 years) and adults with severe allergic asthma more likely to benefit from anti-IgE treatment (conditional recommendation, low quality of evidence).

Remarks: Since these recommendations have not been prospectively evaluated, treatment decisions should consider these biomarker thresholds cautiously, as patients with eosinophil or FeNO values below the proposed cutoffs can still benefit from omalizumab. In addition, these thresholds were largely determined by one particular study (29). Periostin was omitted from these recommendations, as this biomarker is not clinically available, and it is not useful in children < 12 yrs because it is also produced from growing bone.

Remarks

The recommendation places a high value on an increased treatment response when blood eosinophil and FeNO are used to select patients and a low value on the use of periostin.

Should a long-acting inhaled muscarinic antagonist (LAMA) be used in adults and children with severe asthma?

Summary of the evidence

We identified three randomized, placebo-controlled trials in adults 18-75 years of age, one crossover and two parallel designs; one trial in adolescents (age 12-17

years), and one trial in children (age 6-11 years) (36-38). These trials included individuals with severe uncontrolled asthma on GINA step 4-5 or NAEPP step 5 therapies. Adults were treated with at least a high-dose ICS in combination with a long-acting beta2-adrenergic receptor agonist while adolescents and children were treated with medium-dose ICS and LABA with a third controller.

In the adolescent and pediatric studies, eligible patients were randomized in a 1:1:1 ratio to receive tiotropium 5 ug (two puffs of 2.5 ug) or 2.5 ug (two puffs of 1.25 ug) or placebo (two puffs), each delivered for 12 weeks via the Respimat Soft Mist inhaler as add-on to pre-enrollment background therapy with ICS plus one or more controller therapies. Whereas two adult studies (37) compared 5 ug tiotropium (2 puffs of 2.5 ug) delivered by Respimat over 48 weeks to placebo; one adult study (36) involved an 8 week, three-way crossover design with 5 ug tiotropium (2 puffs of 2.5 ug), 10 ug triotropium (2 puffs of 5 ug) and placebo and was excluded from further analyses and the primary meta-analyses. The remaining four trials enrolled a total of 1,433 participants (2.5 ug dose, n=528) and were pooled for meta-analyses to inform the Task Force's judgments.

Across the four parallel arm trials including children, adolescents, and adults, the addition of tiotropium 5ug resulted in improvements in mean peak FEV_1 response compared to placebo (123 ml [95%CI = 88.2, 158.7]), which was statistically significant but a clinically trivial difference. Serious imprecision in the certainty estimates was also noted for each age group. The addition of tiotropium 5 ug also

marginally improved ACQ-7 (-0.11 [95%CI = -0.2, 0.01]) and prevented asthma worsening (based on exacerbations or symptoms, RR=0.79 [95%CI = 0.7, 0.89]; AR 133 fewer worsening episodes per 1,000 [95CI% 54 – 122]) compared to placebo, but again, serious imprecision in the certainty estimates was noted for children and adolescents. In children and adolescents, addition of tiotropium 2.5ug did not improve asthma control scores but did improve FEV_1 % predicted (MD, 4.99 [95%CI = 2.84, 7.15] and reduced asthma worsening (RR=0.66 [95%CI = 0.45, 0.97]. *Post hoc* analyses of adjusted mean trough FEV_1/FVC responses in children also demonstrated statistically significant improvements at all-time points versus placebo with both tiotropium doses, with the exception of tiotropium 2.5 mg at week 8.

In the two adult trials, treatment with tiotropium 5 ug did not result in significant differences in AQLQ (MD, 0.10 [95%CI = -0.04, 0.23] but did increase the time to first exacerbation requiring OCS (HR for placebo, 0.79 [95%CI = 0.62, 1.01]). Asthma exacerbations requiring hospitalization were too infrequent in both the tiotropium (16 of 453 subjects) and placebo (20 of 454) arms to draw conclusions (37). The cross-over study in adults (36) that was excluded from the primary analysis, similarly noted beneficial effects of tiotropium 5 ug (MD, 139ml [95%CI = 96, 181ml]) and 10 ug (MD, 170ml [95%CI = 128, 213]) on peak FEV_1 response in adults.

Adverse events were less frequent in the tiotropium arms compared to placebo in these four trials (RR=0.92 [95%CI=0.86-0.98]. Severe adverse events were equally infrequent across treatment arms.

Benefits

Long-acting muscarinic antagonist treatment in children, adolescents and adults with severe asthma may improve FEV_1 and may reduce loss of asthma control. In adults, treatment with tiotropium 5 ug also improves asthma control and increases time to the first exacerbation.

Harms

There was a lower frequency of adverse events in children, adolescents and adults treated with tiotropium 5 ug compared to placebo. The frequency of severe adverse events was also low and nearly equal to placebo.

Conclusions and research needs:

The addition of tiotropium improves FEV_1 and provides beneficial effects on symptom control in children, adolescents, and adults with severe asthma not controlled with GINA step 4-5 and NAEPP step 5 combination therapies. There were too few severe exacerbations requiring OCS to draw definitive conclusions as to benefit. Based on the estimated beneficial effects observed for tiotropium, the Task Force judged that these benefits outweigh the adverse effects, burdens, and costs associated with this treatment for the management of severe asthma.

In the combined age groups, tiotropium was effective in preventing the composite outcome for asthma worsening inclusive of symptom control and exacerbations. However, the effect of treatment was not significant in adolescents and children likely due to the smaller sample sizes and shorter study duration of these trials. There is insufficient evidence for the beneficial effects of tiotropium on severe exacerbations in children and adolescents with severe asthma, which should be investigated in longer-term trial cohorts of sufficient size. There are additional long-acting muscarinic antagonists (umeclidinium, glycopyrronium) currently available which could be alternative long-term bronchodilator therapies for severe asthma. Treatment with umeclidinium and glycopyrronium have beneficial effects on lung function and symptom control in individuals with mild-to-moderate, persistent asthma (39-41), but have not been evaluated as an adjunct therapy for severe asthma.

Future studies should also focus on the identification of severe asthma subgroups preferentially responsive to long-acting muscarinic antagonists that might benefit from the step-wide addition of muscarinic antagonists compared to alternative step-up options such as long-acting beta agonists or increased ICS dosing. Subgroup analyses of trial cohorts with mild-to-moderate persistent asthma subjects have suggested that subgroups with fixed or baseline airflow obstruction might preferentially respond to long-acting muscarinic antagonists (41, 42). Three randomized-controlled trials only included subjects with an FEV_1<80% predicted. Kerstjens and colleagues showed beneficial effects in both those with screening FEV_1<60% or 60-80% predicted(43). Two trials in children and adolescents

enrolled asthma patients with an FEV_1 between 60-90% predicted (38, 44). Hence, it is not clear whether individuals, particularly adults, with severe asthma and higher lung function on combination therapy with high-dose inhaled glucocorticoids and a long-acting beta agonist will benefit from the addition of a long-acting muscarinic antagonist.

A responder analysis of a severe asthma trial cohort showed equally beneficial effects when comparing subgroups based on baseline lung function, age, sex, ethnicity, BMI, and racial groups. Differential inter-racial effects are difficult to ascertain since minority racial groups (African Americans and Asians) and Hispanic ethnic groups represented the vast minority of subjects in these trials (43). Future trials in increasingly ethnically diverse severe asthma cohorts should provide insight into the beneficial effects of long-acting muscarinic antagonists in these groups, which experience a substantial proportion of asthma-related morbidity. Studies to evaluate responder subgroups based on genetic variation (pharmacogenetic studies) should also be performed using DNA samples from prior and future clinical trials.

What others are saying:

GINA guidelines for the Diagnosis of Management of Severe Asthma published in 2018 recommend the use of tiotropium as an add-on therapeutic option at step 4 or 5 for patients with exacerbations despite treatment with ICS and LABA. The NAEPP guidelines do not outline any role for the muscarinic antagonists.

ATS/ERS recommendation

For children, adolescents, and adults with severe asthma uncontrolled despite GINA step 4-5 or NAEPP step 5 therapies, we recommend the addition of tiotropium (strong recommendation, moderate quality of evidence).

Remarks

While the taskforce only found data on the efficacy of 5ug in adults with severe asthma, the effects on lung function were similar to the FDA-approved 2.5ug and 5mcg doses evaluated in parallel, placebo-controlled trials of adults with mild-moderate asthma. In addition, clinical trials in adolescents with moderate and severe asthma showed that the 2.5 and 5ug doses were similarly effective. This recommendation places a high value on improving symptom control and reducing exacerbations. The strength of the recommendations is based on the following considerations when comparing the addition of tiotropium versus no addition. The evidence suggested with moderate certainty a large benefit and trivial harm with the balance of effects clearly favoring the intervention. Tiotropium was considered probably acceptable and probably feasible to implement. This recommendation also accounts for the feasibility of this inhaled therapy compared to the cost and burden of alternative add-on biologic therapies for severe asthma.

Should a macrolide (i.e., azithromycin, clarithromycin) be used in adults and children with severe asthma?

Summary of the evidence

The previous ERS/ATS guidelines made a conditional recommendation that long-term macrolide antibiotics should *not* be used in the treatment of adults or children with severe asthma, based on available evidence. Since then, 6 RCTs have been conducted (45-50), of which 5 included only adults and 1 included only children 6 to < 18 years of age. There were varying definitions of persistent symptomatic or uncontrolled asthma, and none met ERS/ATS criteria for severity. Three studies used azithromycin; of these, two (totaling 529 participants) used doses ranging from 250 mg to 500 mg three times per week for a treatment period of 26 – 48 weeks(45, 46). The other (n=97) used a dose of 600mg/day for 3 days and 600mg/week thereafter for 11 weeks(48). The clarithromycin RCTs (totaling 171 participants) used 600mg twice daily ranging from 8 to 16 weeks in treatment duration(49, 50). In children (n=55), azithromycin nightly doses were given according to body weight, ranging from 250 mg for 25 – 40kg and 500mg for > 40kg for a total of 12 months (the study was prematurely terminated at 30 weeks due to lack of clinical efficacy) (47).

Compared to placebo, during 48 weeks of follow up, azithromycin reduced the number of combined moderate and severe exacerbations (1.07 vs. 1.86 events/patient/year; RR=0.59; 95% CI 0.47, 0.74)(46). Additionally, macrolides reduced the number of patients with at least one moderate or severe asthma exacerbation and the time to first exacerbation. It did not, however, reduce the rate of severe exacerbations (25.3% vs. 34.6%; RR 0.77; 95%CI 0.44, 1.34) in children or adults, during a follow up period ranging from 24 – 48 weeks (45-47). Neither

azithromycin nor clarithromycin treatment improved ACQ-7 (MD 0.11; 95%CI -0.34, 0.12) or AQLQ (MD 0.16; 95%CI -0.06, 0.37) in adults beyond the MCID.

Relative to placebo, treatment with azithromycin or clarithromycin in adults or children was not associated with changes in postbronchodilator FEV_1% predicted (MD 1.95; 95%CI -2.42, 6.32) or prebronchodilator FEV_1 L (MD 0.37; 95%CI -2.17, 2.91) that reached the MCID (45, 48, 49).

The effects of clarithromycin on airway inflammation were inconsistent with only one of two studies showing significant reductions in airway neutrophilia(50).

Compared to placebo, macrolide therapy in adults was associated with a lower number of lower respiratory tract infections requiring antibiotics (20.9% vs. 35.6%; RR 0.60; 95%CI 0.45, 0.79)(45, 46).

The number of study participants with at least 1 adverse event (67.3% vs. 72.2%; RR 0.93; 95%CI 0.73, 1.19) and the number of serious adverse events (9.1% vs. 11.4%; RR 0.81; 95%CI 0.52, 1.24) in adults or children, were not different from placebo(45, 46, 48, 49).

Benefits

Macrolides reduce the number of asthma exacerbations, and at least one study suggests that this effect is similar for participants with or without eosinophilia(46).

The effect on asthma control and quality of life does not reach the MCID.

Harms

Chronic macrolide therapy has been associated with increased incidence of diarrhea; however, the number of serious adverse events or number of participants with at least 1 adverse event is not different to placebo. Although macrolides have a potential risk for QT prolongation or hearing loss, the frequency of these events are not reported to be higher than in the placebo arm in patients whom at baseline had no hearing deficits or abnormally prolonged QTc (46). Relative to placebo, the prevalence of nasal and oropharyngeal macrolide-resistant *Streptococcus* increased in one study (45) but not in another (46). Those treated with azithromycin for 48 weeks, had reduced airway *H. influenzae* load, with no changes to total or pathogenic bacterial loads. Although sputum macrolide resistance genes increased in this group, there was a lower rate of antibiotic use and of adverse events due to clinically diagnosed infections (46, 51).

Conclusions and research needs

Relative to placebo, chronic macrolide therapy reduces the risk of having an asthma exacerbation. However, there is no conclusive evidence that treatment shows any effect in reducing severe exacerbations or hospitalisations. The effects of macrolides on asthma has been limited to participants with uncontrolled or persistently symptomatic disease that may or may not be exacerbation prone; therefore, it is unknown whether this therapy will improve outcomes among those meeting ERS/ATS criteria for severe asthma. The emergence of antimicrobial resistance associated with prolonged antibiotic use such as macrolide therapy is a critical public health issue. Potential benefits in severe asthma need to be carefully

considered against this background risk from both the perspective of an individual patient and the wider community.

What others are saying

GINA guidelines recommend prescribing add-on low-dose macrolide in patients who do not respond to standard treatment, but classify its use off-label and suggest weighing the benefits against the potential for antibiotic resistance. In the BTS/SIGN 2016 guidelines , the use of macrolide antibiotics in asthma was not recommended; new guidelines for the long-term use of macrolides are under preparation. The FDA has not approved the use of chronic macrolide therapy for asthma.

ERS/ATS Recommendation

We suggest a trial of macrolide treatment to reduce asthma exacerbations in adult asthmatics on GINA/NAEPP step 5 therapy that remain persistently symptomatic or uncontrolled (conditional recommendation, low quality of evidence)

We suggest against the use of chronic macrolide treatment in children and adolescents with severe uncontrolled asthma (conditional recommendation, low quality of evidence).

Remarks: This recommendation is conditional and based on the need to avoid exacerbations and reduce OCS. The benefits and safety of using macrolides for asthma beyond 1 year has not been determined.

Should an anti-interleukin 4/13 strategy be used for adults and children with severe asthma?

Summary of the evidence

Dupilumab is a fully human monoclonal antibody directed against the alpha subunit of interleukin-4 receptor. It blocks signaling of two key type-2 cytokines; IL-4 and IL-13. We identified three randomized, placebo-controlled trials evaluating dupilumab as add-on therapy in patients with moderate-to-severe asthma (52-54). Two RCTs included adolescent (ages 12-17) and adult (age ≥18 years) participants (53, 54) and one trial included only adult participants (52).

In the phase 2b dose-ranging clinical trial (52), four dosing regimens of dupilumab were studied: 200 or 300 mg of the drug administered subcutaneously every 2 or 4 weeks for 24 weeks. 769 adult patients with uncontrolled asthma, despite use of medium to high dose ICS and LABA, were randomized 1:1:1:1:1 into four treatment arms or placebo. Primary endpoint was change in FEV_1 (L) at 12 weeks in patients with blood eosinophil counts of at least 300 cells/mm^3. Prespecified secondary endpoints at weeks 12 & 24 included asthma exacerbation rate, time to severe

exacerbation, asthma symptom score, asthma quality of life and change in FEV_1 (%predicted).

One phase 3 efficacy and safety RCT (53) was in adolescents and adults with moderate to severe uncontrolled asthma and it evaluated dupilumab add-on therapy at doses 200 mg (after a loading dose of 400mg) or 300 mg (after a loading dose of 600 mg) every 2 weeks for 52 weeks. A total of 1902 participants were randomized 2:2:1:1 with matched volume placebo. The primary endpoints were annualized exacerbation rates (week 52) and absolute change in FEV_1 (week 12). Secondary endpoints included change in FEV_1% predicted, ACQ, AQLQ as well as subgroup analysis by blood eosinophil count.

The second phase 3 RCT (54) evaluated dupilumab (300 mg every 2 weeks for 24 weeks) in 210 adolescents and adults with severe oral glucocorticoid-dependent asthma. After a steroid dose-optimization period, patients were randomized 1:1 to receive dupilumab or placebo. OCS dose was adjusted down during weeks 4-20. Primary endpoint was percent reduction in OCS dose required to maintain asthma control. Secondary endpoints included proportion of patients with at least 50% reduction in OCS dose and proportion of patients with reduction in OCS dose to <5 mg/d.

These three trials were pooled for meta-analysis (see evidence profiles in the supplementary material). Effects of dupilumab on exacerbation rate, asthma control, asthma quality of life, lung function and side effects were assessed for 200mg and

300mg doses at 24 and 52 weeks. Differences in effect size by blood eosinophils were also assessed.

Relative to participants assigned to placebo, those assigned to dupilumab (200 mg or 300 mg every 2 weeks; 24 and 52 weeks) experienced substantial (46-70.5%) reduction in annualized rates of asthma exacerbations. Dupilumab therapy resulted in greater proportion of participants with OCS-dependent severe asthma experiencing > 50% reduction in OCS dose (relative risk [RR]1.49; 95% Ci 1.22-1.83; AR 26 more achieved 50% reduction per 100 [95%CI 12 – 44]), reduction in OCS dose to < 5mg/d (RR 1.92; 95%CI 1.46-2.53; AR 344 more per 1,000 [95%CI 172 – 572]) and discontinuation of maintenance OCS (RR 1.81; 95%CI 1.28-2.57). Improvements in FEV_1, ACQ-5 and AQLQ were statistically significant but did not reach MCID.

The effect size for all above outcomes was larger in patients with blood eosinophil counts $\geq$ 300 cells/mm^3 when compared with eosinophils <300 cells/mm^3 (see evidence profiles in supplementary material). One study further stratified the study cohort by blood eosinophils <150 cells/mm^3, 150-300 cells/mm^3 and $\geq$ 300 cells/mm^3 (53). Rate ratio for annualized severe exacerbation event rate at 52 weeks, pooled for doses 200 and 300 mg every 2 weeks, was 0.33 (95% CI 0.26-0.42); 0.386 versus 1.158 events/patient/year for subgroup with blood eosinophils $\geq$ 300 cells/mm^3, 0.60 (96% CI 0.43-0.83); 0.515 versus 0.855 events/patient/year for blood eosinophils 150 - 300 cells/mm^3 and 1.04 (95% CI 0.76-1.43); 0.604

versus 0.576 events/patient/year for blood eosinophils < 150 cells/mm^3. The same study reported similar results for exacerbations and lung function when stratified by FeNO ≥50 ppb, ≥ 25-<50 ppb and <25 ppb. A post-hoc biomarker interaction analysis found the greatest treatment response in patients with FeNO ≥ 25 ppb and blood eosinophils ≥ 150 cells/mm^3.

Benefits

Dupilumab, as add-on therapy in patients with asthma that is uncontrolled on medium-high dose ICS + LABA, may reduce exacerbations and improve asthma symptoms and lung function. The efficacy is greater in patients with type 2 biomarkers (blood eosinophils > 150 cells/mm^3 or FeNO > 25 ppb) Dupilumab may reduce OCS dose in patients with severe CS-dependent asthma.

Harms

The risk of dupilumab therapy appears to be small with injection site reaction as the most common treatment related adverse effect. Frequency of serious and any side effects were similar with dupilumab when compared with placebo. However, the mechanisms and potential clinical significance of treatment-related transient blood eosinophilia is not fully understood and needs further elucidation. Because dupilumab-mediated eosinophilia has not been associated with adverse events, there are no specific monitoring recommendations.

Conclusions and research needs

Dupilumab add-on therapy substantially decreases exacerbations in moderate to severe uncontrolled asthma (52-54). It is effective in reducing OCS dose in patients with severe OCS-dependent asthma. Dupilumab therapy is also associated with improvements in lung function, asthma control and quality of life. More robust improvements were observed in patients with greater eosinophil levels.

Ongoing and future studies should provide additional information on long-term safety and durability of response to dupilumab therapy. More data on efficacy and safety are also needed in children and adolescents. Future studies should also focus on identifying specific disease and population characteristics that can predict response to this therapy.

What others are saying

GINA recommends dupilumab as add-on option for patients with severe eosinophilic or Type-2 asthma uncontrolled on high dose ICS-LABA, or requiring maintenance OCS. NICE guidelines do not currently include dupilumab as add-on therapeutic option for asthma.

ERS/ATS recommendation

We suggest dupilumab as add-on therapy for adult patients with severe eosinophilic asthma, and for those with severe corticosteroid-dependent asthma regardless of eosinophil levels (conditional recommendation).

Remark: These recommendations place a high value on reducing exacerbations and steroid exposure and a lower value on cost or burden of the intervention.

The high cost of dupilumab and its impact on cost effectiveness, equity and feasibility to implementation must be weighed by clinicians in relation to its benefits on asthma outcomes). Due to limited number of adolescents treated with anti-IL4/13, the TF was unable to provide a recommendation for this age group and no available evidence exists for children < 12 yrs.

Discussion

The ERS/ATS severe asthma Task Force evaluated 6 questions that were not addressed in previous guidelines. We conducted a systematic literature search and GRADE analysis to inform recommendations for each specific PICO question regarding the management of severe asthma. The balance of benefits versus burdens, adverse effects and costs; the quality of evidence; the feasibility and the acceptability were all considered in developing each recommendation (See Table 2) A conditional recommendation was made for the use of anti-IL5 & anti-IL4/13 strategies for severe uncontrolled eosinophilic phenotype. Anti-IL4/13 is also indicated for systemic corticosteroid dependent severe asthmatics regardless of eosinophilic status. Specific eosinophil and FeNO cutoffs were recommended to identify those with the greatest likelihood or response to anti-IL5 or anti-IgE therapy. The use of inhaled tiotropium was recommended for adolescents and adults with severe asthma uncontrolled despite GINA step 4-5 or NAEPP step 5 therapies. A trial of chronic macrolide therapy was conditionally suggested to reduce asthma exacerbations in persistently symptomatic or uncontrolled patients on GINA step 5 or NAEPP step 5 therapies. These recommendations should be reconsidered when new evidence becomes available.

It has long been appreciated that the conventional requirements for a good randomised controlled clinical trial do not reflect the reality of patients seen in the clinics(55-57). Stringent diagnostic requirements are imposed, for example in adults

often smoking asthmatics are excluded to avoid an inadvertent mis-diagnosis of COPD. However, this is illogical; non-smokers also get COPD, and those who smoke and have asthma may be more steroid resistant and thus more, not less likely to profit from biologicals. Frequently there is a requirement for acute bronchodilator reversibility to be demonstrated, even though this is not predictive of a response to treatment and there is no uniform definition.

There could be two reasons for excluding a severe asthmatic patient from a trial of (for example) an anti-type-2 monoclonal(55, 57). The first entirely logical reason, would be the absence of any evidence of type-2 activity, and the second, far more dubious, the presence of type-2 activation but a co-existent disqualification such as smoking or the absence of variable airflow obstruction. The Wessex group recently evaluated 37 RCTs of type-2 biologicals, and found that just fewer than 10% of all their patients could have been enrolled, commonest reasons for exclusion being failure to demonstrate either or both of fixed and variable airflow obstruction(55). The exclusion rate for patients with eosinophilic asthma was even higher. In the accompanying editorial(58), it was argued that the right approach for future trials of, for example, anti-type-2 strategies, would be to include all those with the treatable trait of airway eosinophilia, irrespective of whether there were any other features of asthma present. This is in line with the approach advocated by the *Lancet* commission(57), and also the finding of benefit of anti-type-2 strategies in 'eosinophilic COPD'(59, 60). Fortunately the licensing authorities have taken the approach of focusing on the treatable trait of airway eosinophilia, because

otherwise, many patients who could benefit would not have access to these medications. It would be important in post-marketing surveillance, which should be mandated for expensive medications, to confirm that features such as smoking and fixed airflow obstruction do not affect response to therapy.

Another important question arising is whether only patients with genuine severe, therapy resistant asthma should be eligible for biologicals. The initial ERS-ATS Task Force definition, as with so many others, defined severity by the level of prescribed treatment in association with adverse outcomes such as asthma, chronic symptoms and risk. Inherent in the definition is that adherence to medication has been checked and found to be adequate. However, it is increasingly clear that patients prescribed much lower doses of medication are at risk of asthma attacks and death. In the UK National Review of Asthma Deaths(61, 62), around 60% of those who died did not meet ERS-ATS criteria for severe asthma. Important factors, as well as the expected positive predictive effect of a previous acute attack, were: under-use of ICS, over use of short-acting β-2 agonists, and failure to engage with regular monitoring visits. Severe asthma specialty clinics can help these patients become well controlled by addressing reversible factors like poor adherence. However, there are a hard core of patients, termed 'refractory difficult asthma' who continue with poor adherence and other risk-taking activities despite multiple interventions; in other words, adherence has been optimized as far as possible, but is still inadequate. It has been argued elsewhere that such children – or other non-adherent patients – should be offered biologicals if they have the necessary

treatable airway trait, to prevent asthma deaths(63, 64). The same argument has been advanced in adults. This is not a group that are included in randomised controlled trials, so we cannot make evidence based recommendations. However, it seems not unreasonable that a persistent treatable trait, whether steroid resistant or uncontrolled because of social factors, should be treated the same way irrespective of cause. However, the condition of giving biologicals to the non-adherent must be that it is directly observed in hospital, such patients cannot be a candidate for home therapy.

A future challenge is to ensure that children who might benefit from biologicals actually receive them. There are clear phenotypic differences between paediatric and adult asthma(65), and although atopy is very common in severe paediatric asthma, it is by no means clear that airway eosinophilia is necessarily type-2 driven(66). Indeed, even in adult asthma, non-type-2 eosinophilic endotypes are being discovered(67). Also, there is reason to suppose that anti-eosinophil strategies may be deleterious in children, given the role of the eosinophil in immune homeostasis(68). There are extensive paediatric data on efficacy and safety of the anti-IgE monoclonal omalizumab(69-71), so there should be no reason not to replicate these studies for other anti-IL5 trategies, in the absence of a reliable biomarker of efficacy. In summary, it is essential to do paediatric trials of these new agents that evaluate the impact of these treatments on development and long-term outcomes, and also to pursue research into biomarkers of efficacy(72).

There is another troubling aspect concerning the application of biologicals in children. The conventional sequence of medication testing is in adults first, and then if safety and efficacy is demonstrated, performing studies in children. If there is no efficacy in adults, then the medication is not tested further. An obvious example is the anti-IL13 monoclonal Tralokinumab(73, 74). At least three randomised controlled studies in adults failed to show significant clinical efficacy(75-77), and there are no plans to do a paediatric trial, on the basis that the data shows that the IL13 pathway is not crucial in airway eosinophilia. It is true that adolescents age over 12 years are included in these studies, but the actual numbers enrolled are dwarfed by adult participants. Although this seems a logical conclusion in adults, there are no data to confirm or refute this in children; is it conceivable that a potentially valuable paediatric monoclonal has been discarded wrongly? It would be very difficult to prioritise a paediatric Tralokinumab trial at present, but it does highlight the need to better understand the similarities and differences between adult and paediatric endotypes.

Although this document has reviewed a large body of high quality evidence, and highlighted new evidence that OCS dose and asthma attack risk can be substantially reduced, there is much work still to be done. Mepolizumab, benralizumab and reslizumab all target the type-2 pathways, and it is more than likely that further similar compounds will be licensed. The question that arises is, how to determine which of an overlapping series of biologicals should be prescribed for the individual patient. Although the majority of studies reviewed here focused on peripheral

eosinophils as a marker of type-2 inflammation, other biomarkers such as FeNO could offer additional information in identifying sub-endotypes. We speculate that additional type-2 pathway biomarkers will need to be identified in order to do this effectively, and in this regard, the systematic analyses of existing severe asthma cohorts such as SARP and U-BIOPRED will be invaluable. Although group data may show one or other is marginally better, it is inconceivable that one will be superior for all individuals. Of course, a series of N-of-1 trials can be carried out, but this is hardly scientific therapeutics. Furthermore, combination of biologics may prove to be better on the speculation e that Type 2 inflammation may be most effectively abrogated by blocking all the signature type-2 cytokines, IL4, IL5 and IL13 with dupilumab combined with an anti-IL-5 or anti-IL5Ra strategy. Pragmatic clinical trials may potentially provide answers to these questions for real-life clinical practice(78).

Another future challenge is the role of biologicals in low and middle income (LMIC) settings, as the majority of data derive from a developed world setting. There may well be different asthma endotypes across the world, and more importantly, the significance of a raised blood eosinophil count in a region with a high burden of parasitic infections may be different. The WHO defined three groups of severe asthma of which untreated severe asthma is most relevant to LMIC(79). The first priority must be to ensure that basic asthma medications are uniformly available across the world, which will then enable us to obtain data on the true prevalence of severe, therapy resistant asthma and refractory difficult asthma in a LMIC setting. The most difficult challenge will be the cost of these medications, and making them

available to those who would benefit outside a resource-rich area. This challenge is not of course unique to asthma.

Finally, most of the work on the new asthma therapies has been on their role in preventing asthma attacks, where they have been very successful. In the future, they may have a role in the aftermath of an acute asthma attack. Provided the patient reaches an emergency facility in time, the basic treatment of an asthma attack is straightforward. Much more difficult is to prevent a further attack, and it has been highlighted that the period of highest risk is in the month after the signal attack(61, 62). Given that outside the pre-school years, asthma attacks are caused by respiratory viral infection on the background of uncontrolled type-2-driven airway inflammation, and anti-type-2 strategy as a single injection might well be a promising strategy to reduce relapse, especially as it would not require adherence, and would potentially be efficacious to buy time while other social and environmental factors are addressed. More data are needed before this strategy can be recommended.

In summary, the PICOs studied here have enabled the Task Force to make recommendations for the treatment of severe asthma, which should lead to modifications of guidelines and improvement in outcomes which are important to patients, namely reduction in OCS dose and exacerbation frequency, and improved quality of life. However, we recognize that these recommendations will not be effective across all severe asthmatics and that more precise phenotype-driven

research is needed. We also reiterate that, prior to adopting these novel and in many cases invasive and expensive approaches, every effort should be made to deploy standard medications to maximum benefits. However for the minority of patients with asthma who, for whatever reason, do not respond to standard therapies and continue to experience frequent exacerbations, we are in an exciting new and evolving world of novel, beneficial approaches.

Table 2. Task Force recommendations for the management of severe asthma

Recommendation	Strength	Quality of evidence
We suggest anti-IL5 strategy as add-on therapy for adult patients with severe uncontrolled asthma with an eosinophilic phenotype and for those with severe corticosteroid-dependent asthma	Conditional	Varied by treatment*
We suggest that a blood eosinophil cut-point of ≥ 150/μl can be used to guide anti-IL5 initiation in adult patients with severe asthma and prior exacerbations.	Conditional	Low
We suggest using a blood eosinophil cut-off of ≥ 260 /μl to identify adolescents (>12 years) and adults with severe allergic asthma more likely to benefit from anti-IgE treatment	Conditional	Low
We suggest using a FeNO cut-off of ≥ 19.5 ppb to identify adolescents (>12 years) and adults with severe allergic asthma more likely to benefit from anti-IgE treatment	Conditional	Low
For children, adolescents, and adults with severe asthma uncontrolled despite GINA step 4-5 or NAEPP step 5 therapies, we recommend the addition of tiotropium	Strong	Moderate
We suggest a trial of macrolide treatment to reduce asthma exacerbations in adult asthmatics on GINA/NAEPP step 5 therapy that remain persistently symptomatic or uncontrolled. We suggest against the use of chronic macrolide treatment in children and adolescents with severe uncontrolled asthma	Conditional	Low
We suggest dupilumab for adult patients with severe eosinophilic asthma, and for those with severe corticosteroid-dependent asthma regardless of eosinophil levels	Conditional	Low

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GRADE Evidence profiles and Evidence to Decision Frameworks, Severe Asthma Task Force.

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Should a monoclonal anti-IL5 antibody be used in adults and children with severe asthma?

GRADE Evidence Profile: MEPOLIZUMAB

Bibliography[a]: Bel 2014, Chupp 2017, Ortega 2014

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Mepolizumab**	**placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Quality of life (change from baseline) (follow up: range 24 weeks to 32 weeks; assessed with: St George's Respiratory Questionnaire; Scale from: 0 to 100; higher scores indicate more limitations; MCID 4 units)												
3 [1,2,3]	randomised trials	not serious	not serious	not serious [b]	not serious	none	537	534	-	MD **7.14 lower** (9.07 lower to 5.21 lower)	⊕⊕⊕⊕ HIGH	CRITICAL
Asthma control (change from baseline) (follow up: range 24 weeks to 32 weeks; assessed with: Asthma Control Questionnaire (ACQ-5); Scale from: 0 to 6; lower values indicate better asthma control; MCID 0.5)												
3 [1,2,3]	randomised trials	not serious	not serious	not serious [b]	serious [c]	none	537	534	-	MD **0.43 lower** (0.56 lower to 0.31 lower)	⊕⊕⊕◯ MODERATE	CRITICAL
Asthma symptoms (change from baseline) (follow up: 24 weeks; assessed with: Asthma symptom score; Scale from: 0 to 5; higher scores indicate more frequent symptoms and more limitations)												
1 [2]	randomised trials	serious [d]	not serious	not serious [e]	not serious	none	266	259	-	MD **0.2 units lower** (0.03 lower to 0.37 lower)	⊕⊕⊕◯ MODERATE	CRITICAL
Lung function (Pre-bronchodilator FEV1 % predicted) (follow up: range 24 weeks to 32 weeks; MCID 10.38%[4])												
2 [1,3]	randomised trials	serious [f]	not serious	not serious [b]	not serious [g]	none	Graphs presenting results from Bel 2014 and Ortega 2014 showed the mepolizumab group had higher FEV1 % predicted than the placebo group at the end of the studies, however the 95% CI around the central estimate from each treatment arm overlap. This suggests the difference between groups in non-significant.				⊕⊕⊕◯ MODERATE	IMPORTANT
Lung function (Pre-bronchodilator FEV1 litres, change from baseline) (follow up: range 24 weeks to 32 weeks; MCID 0.23 litre[4])												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mepolizumab	placebo	Relative (95% CI)	Absolute (95% CI)		
2 [1,2]	randomised trials	not serious	not serious	not serious [b]	not serious [h]	none	468	468	-	MD **0.11 higher** (0.06 higher to 0.17 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT
Lung function (Post-bronchodilator FEV1 litres, change from baseline) (follow up: range 24 weeks to 32 weeks; MCID 0.23 litre[4])												
3 [1,2,3]	randomised trials	serious [i]	not serious	not serious [b]	not serious	none	Ortega 2014 reported the mean difference from placebo (95%CI) = 0.138 L (0.043 to 0.232 L), P = 0.004. Two studies reported a non-significant difference favouring mepolizumab: Bel 2014, (0.128 L, P = 0.06) and Chupp 2017 (data not shown).				⊕⊕⊕◯ MODERATE	IMPORTANT
Rate of any exacerbation (follow up: range 24 weeks to 32 weeks)												
3 [1,2,3]	randomised trials	not serious	not serious	not serious [b]	not serious	none	537	534	**Rate ratio 0.50** (0.39 to 0.65)	Incidence rate (events/patient/year): mepolizumab 0.92; placebo 1.69	⊕⊕⊕⊕ HIGH	CRITICAL
Time to first asthma exacerbation (follow up: 32 weeks)												
1 [1]	randomised trials	not serious	not serious	not serious [j]	not serious	none	**Hazard ratio** (95% CI) (mepolizumab/placebo) = 0.44 (0.32, 0.60), p <0.001. Number of patients: 194 (mepolizumab) and 191 (placebo).				⊕⊕⊕⊕ HIGH	CRITICAL
Rate of exacerbations requiring emergency department visit or hospitalisation (follow up: range 24 weeks to 32 weeks)												
2 [1,2]	randomised trials	not serious	not serious	not serious [b]	not serious	none	468	468	**Rate ratio 0.36** (0.20 to 0.66)	Incidence rate (events/patient/year): mepolizumab 0.05; placebo 0.15	⊕⊕⊕⊕ HIGH	CRITICAL
Rate of exacerbations requiring hospitalisation (follow up: range 24 weeks to 32 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mepolizumab	placebo	Relative (95% CI)	Absolute (95% CI)		
2 [1,2]	randomised trials	not serious	not serious	not serious [b]	not serious	none	468	468	**Rate ratio 0.31** (0.13 to 0.73)	Incidence rate (events/patient/year): mepolizumab 0.02; placebo 0.07 (from Chupp 2017)	⊕⊕⊕⊕ HIGH	CRITICAL
Adverse events (follow up: range 24 weeks to 32 weeks)												
3 [1,2,3]	randomised trials	not serious	not serious	not serious [b]	not serious [k,l]	none	401/536 (74.8%)	426/535 (79.6%)	**RR 0.93** (0.88 to 0.99) [k]	**56 fewer per 1,000** (from 8 fewer to 96 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Drug-related adverse events (follow up: range 24 weeks to 32 weeks)												
3 [1,2,3]	randomised trials	not serious	not serious	not serious [b]	not serious [l]	none	91/536 (17.0%)	67/535 (12.5%)	**RR 1.35** (1.01 to 1.80)	**44 more per 1,000** (from 1 more to 100 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Serious adverse events (follow up: range 24 weeks to 32 weeks)												
3 [1,2,3]	randomised trials	not serious	not serious [m]	not serious [b]	not serious [n]	none	32/536 (6.0%)	62/535 (11.6%)	**RR 0.50** (0.24 to 1.05)	**58 fewer per 1,000** (from 88 fewer to 6 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Systemic steroids (absolute final dose) (follow up: 24 weeks)												
1 [3]	randomised trials	not serious	not serious	not serious	serious [o]	none	Prednisone dose (mg) at study weeks 20-24 were: placebo group, mean (standard deviation, SD) = 10.5 (7.8); median (range) = 10.0 (0-30). Mepolizumab group, mean (SD) = 8.6 (11.9); median (range) = 3.1 (0-67). No statistical test comparing results from the two groups has been reported.[p]				⊕⊕⊕◯ MODERATE	CRITICAL
Systemic steroid (percent reduction) (follow up: 24 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mepolizumab	placebo	Relative (95% CI)	Absolute (95% CI)		
1 [3]	randomised trials	not serious	not serious	not serious	serious [o]	none	Median percent reduction from baseline in daily oral glucocorticoid dose (95% CI): Placebo = 0.0 (-20.0 to 33.3), Mepolizumab = 50.0 (20.0 to 75.0), p = 0.007.[q]				⨁⨁⨁◯ MODERATE	CRITICAL
Loss of work or school days, Intensive care unit admission, Non-invasive ventilation, Intubation, Comorbidities, Upper airway symptoms - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	

CI: Confidence interval; **FEV1:** forced expiratory volume in 1 second; **MCID:** minimal clinically important difference: **MD:** Mean difference; **HR:** Hazard Ratio; **RR:** Risk ratio

Explanations

a. The participants included in the three studies have been considered by the Task Force to represent a population of severe asthmatics as defined by the ERS/ATS Guidelines on Severe Asthma 2014[5].

b. Chupp 2017 and Ortega 2014 inclusion criteria for participants 12-17 years of age required treatment with inhaled corticosteroids at lower doses than those recommended by the ERS/ATS Guidelines on Severe Asthma 2014[5]. The proportion of included participants 12-17 years of age was not specified, however we have assumed this proportion was small relative to each study's total population and therefore we have not downgraded for indirectness.

c. The ends of the 95% confidence interval include appreciable clinical benefit (MCID = 0.5) and no benefit and could lead to different clinical decisions.

d. This outcome has been planned by Bel 2014 and Ortega 2014, as specified in the study protocols, but has not been reported.

e. Chupp 2017 inclusion criteria for participants 12-17 years of age required treatment with inhaled corticosteroids at lower doses than those recommended by the ERS/ATS Guidelines on Severe Asthma 2014[5]. The proportion of included participants 12-17 years of age was not specified, however we have assumed this proportion was small relative to the total study population and therefore we have not downgraded for indirectness.

f. This outcome has been reported incompletely by Bel 2014 and Ortega 2014 so that results cannot be entered in a meta-analysis (high risk of selective outcome reporting bias).

g. The results of the primary studies have been presented in graphical format only and cannot be entered in a meta-analysis. As we have downgraded the rating of risk of bias for this same reason, we have decided not to downgrade the rating of imprecision.

h. Bel 2014 reported the mean difference in pre-bronchodilator FEV1 between the mepolizumab and placebo groups to be 0.114 liters (p = 0.15). These results have been reported incompletely so that they cannot be entered in the meta-analysis. However the sample size on Bel 2014 is the smallest among the three included studies and the effect estimate (0.114) is very close to that from Chupp 2017 and Ortega 2014, so we considered it unlikely that inclusion of Bel's results would change the pooled effect estimate significantly.

i. This outcome has been reported incompletely by Bel 2014 and Chupp 2017 so that results cannot be entered in a meta-analysis (high risk of selective outcome reporting bias).

j. Ortega 2014 inclusion criteria for participants 12-17 years of age required treatment with inhaled corticosteroids at lower doses than those recommended by the ERS/ATS Guidelines on Severe Asthma 2014[5]. The proportion of included participants 12-17 years of age was not specified, however we have assumed this proportion was small relative to the total study population and therefore we have not downgraded for indirectness.

k.There was a high incidence of adverse events in both mepolizumab and placebo groups. The apparent benefit from mepolizumab might be explained by a reduction of asthma-related adverse events with the active drug.

l. This judgement was based on a arbitrary clinical decision threshold of 15% increase or decrease in absolute effect.

m. I^2 = 57% (P=0.10) may represent moderate heterogeneity. However the point estimates from the 3 studies have the same direction of effect and the 95% confidence intervals overlap. For these reasons we have not rated down for inconsistency.

n. This judgement was based on a arbitrary clinical decision threshold of 10% increase or decrease in absolute effect.

o. Single study including only 135 patients.

p. The mean and median from the mepolizumab group are very different (8.6 and 3.1). We have performed data checks (http://handbook-5-1.cochrane.org/chapter_9/9_4_5_3_meta_analysis_of_skewed_data.htm) using the reported mean and standard deviations which indicate a skewed distribution. So we have not used the mean and standard deviation to calculate the mean difference in systemic steroid use.

q. Bel 2014 reported the median difference and associated confidence intervals were calculated with the use of the Hodges–Lehman estimation. P values were calculated with the use of a Wilcoxon rank-sum test.

References

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GRADE Evidence Profile: RESLIZUMAB

Bibliography: Bjermer 2016, Castro 2011, Castro 2015, Corren 2016

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Reslizumab**	**placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Quality of life (change from baseline) (follow up: range 16 weeks to 52 weeks; assessed with: Asthma Quality of Life Questionnaire (AQLQ); Scale from: 1 to 7; higher values indicate better quality of life; MCID 0.5)												
3 [1,2]	randomised trials	not serious	not serious	serious [a]	not serious	none	576	577	-	MD **0.28 higher** (0.17 higher to 0.39 higher)	⊕⊕⊕◯ MODERATE	CRITICAL
Asthma control (change from baseline) (follow up: range 15 weeks to 52 weeks; assessed with: Asthma Control Questionnaire (ACQ-7); Scale from: 0 to 6; lower values indicate better asthma control; MCID 0.5)												
5 [1,2,3,4]	randomised trials	not serious	not serious	serious [b]	not serious	none	1024	727	-	MD **0.26 lower** (0.33 lower to 0.18 lower)	⊕⊕⊕◯ MODERATE	CRITICAL
Asthma control (change from baseline) (follow up: 15 weeks; assessed with: Asthma Control Questionnaire (ACQ-7); Scale from: 0 to 6; lower values indicate better asthma control; MCID 0.5) **Study participants meet criteria for the diagnosis of severe asthma defined by the ERS/ATS Guidelines on Severe Asthma [6]**												
1 [4]	randomised trials	not serious	not serious	not serious	very serious [c]	none	53	53	-	MD **0.4 lower** (0.79 lower to 0.01 lower)	⊕⊕◯◯ LOW	CRITICAL
Asthma symptoms (change from baseline) (follow up: range 16 weeks to 52 weeks; assessed with: Asthma Symptom Utility Index; Scale from: 0 to 1; lower scores indicate worse asthma symptoms; MCID 0.09 [7])												
3 [1,2]	randomised trials	not serious	not serious	serious [a]	not serious	none	578	579	-	MD **0.05 higher** (0.04 higher to 0.06 higher)	⊕⊕⊕◯ MODERATE	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Reslizumab**	**placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Lung function (Pre-bronchodilator FEV1 % predicted, change from baseline) (follow up: 15 weeks; MCID 10.38%[5]) **<u>Study participants meet criteria for the diagnosis of severe asthma defined by the ERS/ATS Guidelines on Severe Asthma[6]</u>**												
1 [4]	randomised trials	not serious	not serious	not serious	very serious [d]	none	52	52	-	MD **8.63 higher** (3.88 higher to 13.38 higher)	⊕⊕◯◯ LOW	IMPORTANT
Lung function (Pre-bronchodilator FEV1 litres, change from baseline) (follow up: range 15 weeks to 52 weeks; MCID 0.23 litre[5])												
5 [1,2,3,4]	randomised trials	not serious	not serious	serious [b]	not serious	none	1024	726	-	MD **0.12 higher** (0.07 higher to 0.17 higher)	⊕⊕⊕◯ MODERATE	IMPORTANT
Lung function (Pre-bronchodilator FEV1 litres, change from baseline) (follow up: 15 weeks; MCID 0.23 litre[5]) **<u>Study participants meet criteria for the diagnosis of severe asthma defined by the ERS/ATS Guidelines on Severe Asthma[6]</u>**												
1 [4]	randomised trials	not serious	not serious	not serious	very serious [e]	none	52	52	-	MD **0.24 higher** (0.09 higher to 0.39higher)	⊕⊕◯◯ LOW	IMPORTANT
Exacerbations (patients with ≥1 exacerbation) (follow up: range 15 weeks to 52 weeks)												
3 [2,4]	randomised trials	not serious	not serious	serious [f]	not serious	none	155/530 (29.2%)	247/529 (46.7%)	**RR 0.63** (0.53 to 0.76)	**173 fewer per 1,000** (from219fewer to 112 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Exacerbations (patients with ≥1 exacerbation) (follow up: 15 weeks) **<u>Study participants meet criteria for the diagnosis of severe asthma defined by the ERS/ATS Guidelines on Severe Asthma[6]</u>**												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Reslizumab	placebo	Relative (95% CI)	Absolute (95% CI)		
1 [4]	randomised trials	not serious	not serious	not serious	very serious [g,h]	none	4/53 (7.5%)	10/53 (18.9%)	**RR 0.40** (0.13 to 1.20)	**113 fewer per 1,000** (from 164 fewer to 38 more)	⊕⊕◯◯ LOW	CRITICAL
Rate of any exacerbation (follow up: 52 weeks)												
2 [2]	randomised trials	not serious	not serious	serious [f]	not serious	none	477	476	**Rate ratio 0.46** (0.37 to 0.58)	Incidence rate (events/patient/year): reslizumab 0.84; placebo 1.81	⊕⊕⊕◯ MODERATE	CRITICAL
Time to first asthma exacerbation (follow up: 52 weeks)												
2 [2]	randomised trials	not serious	not serious	serious [f]	not serious	none	477	476	**HR 0.54** (0.44 to 0.66)	-	⊕⊕⊕◯ MODERATE	CRITICAL
Rate of exacerbations requiring emergency department visit or hospitalisation (follow up: 52 weeks)												
2 [2]	randomised trials	not serious	not serious	serious [f]	serious [g]	none	477	476	**Rate ratio 0.67** (0.39 to 1.17)	Incidence rate (events/patient/year): reslizumab 0.08; placebo 0.12	⊕⊕◯◯ LOW	CRITICAL
Exacerbations requiring emergency department visit (patients with ≥1 exacerbation) (follow up: 15 weeks) **Study participants meet criteria for the diagnosis of severe asthma defined by the ERS/ATS Guidelines on Severe Asthma [6]**												
1 [4]	randomised trials	not serious	not serious	not serious	very serious [g,h]	none	3/53 (5.7%)	4/53 (7.5%)	**Peto OR 0.74** (0.16 to 3.40)	**19 fewer per 1,000** (from 63 fewer to 142 more)	⊕⊕◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Reslizumab	placebo	Relative (95% CI)	Absolute (95% CI)		
Exacerbations requiring hospitalisation (patients with ≥1 exacerbation) (follow up: 15 weeks) **<u>Study participants meet criteria for the diagnosis of severe asthma defined by the ERS/ATS Guidelines on Severe Asthma</u>** [6]												
1 [4]	randomised trials	not serious	not serious	not serious	very serious [g,h]	none	1/53 (1.9%)	0/53 (0.0%)	**OR 3.00** (0.12 to 72.02)	NA	⊕⊕◯◯ LOW	CRITICAL
Adverse events (follow up: range 15 weeks to 52 weeks)												
5 [1,2,3,4]	randomised trials	not serious	not serious [i]	serious [b]	serious [j,k]	none	690/1028 (67.1%)	587/730 (80.4%)	**RR 0.88** (0.81 to 0.96)[k]	**96 fewer per 1,000** (from 153 fewer to 32 fewer)	⊕⊕◯◯ LOW	CRITICAL
Adverse events (follow up: 15 weeks) **<u>Study participants meet criteria for the diagnosis of severe asthma defined by the ERS/ATS Guidelines on Severe Asthma</u>** [6]												
1 [4]	randomised trials	not serious	not serious	not serious	very serious [h,j]	none	38/53 (71.7%)	42/53 (79.2%)	**RR 0.90** (0.73 to 1.13)	**79 fewer per 1,000** (from 214 fewer to103 more)	⊕⊕◯◯ LOW	CRITICAL
Drug-related adverse events (follow up: 16 weeks)												
2 [1,3]	randomised trials	serious [l]	serious [m]	serious [a]	not serious [n]	none	40/498 (8.0%)	24/202 (11.9%)	**RR 0.78** (0.22 to 2.72)	**26 fewer per 1,000** (from 93 fewer to 204 more)	⊕◯◯◯ VERY LOW	CRITICAL
Serious adverse events (follow up: range 15 weeks to 52 weeks)												
5 [1,2,3,4]	randomised trials	not serious	not serious	serious [b]	not serious [o]	none	64/1028 (6.2%)	63/730 (8.6%)	**RR 0.81** (0.57 to 1.14)	**16 fewer per 1,000** (from 37 fewer to 12 more)	⊕⊕⊕◯ MODERATE	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Reslizumab**	**placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Serious adverse events (follow up: 15 weeks) **<u>Study participants meet criteria for the diagnosis of severe asthma defined by the ERS/ATS Guidelines on Severe Asthma[6]</u>**												
1 [4]	randomised trials	not serious	not serious	not serious	very serious [g,h]	none	2/53 (3.8%)	1/53 (1.9%)	**OR 1.97** (0.20 to 19.40)	**18 more per 1,000** (from 15 fewer to 253 more)	⨁⨁◯◯ LOW	CRITICAL
Systemic steroids (absolute final dose), Systemic steroids (percent reduction), Loss of work or school days, Intensive care unit admission, Non-invasive ventilation, Intubation, Comorbidities, Upper airway symptoms - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	

CI: Confidence interval; **FEV1:** forced expiratory volume in 1 second; **MCID:** minimal clinically important difference; **MD:** Mean difference; **OR**: Odds ratio; **RR:** Risk ratio; **HR:** Hazard Ratio; **NA:** Not available

Explanations

a. All studies included a mixed population of patients with moderate and severe asthma.

b. All studies except one (Castro 2011) included a mixed population of patients with moderate and severe asthma.

c. The ends of the 95% confidence interval include appreciable clinical benefit (MCID = 0.5) and no benefit and could lead to different clinical decisions. Results from single study including only 106 patients.

d. The ends of the 95% confidence interval include appreciable clinical benefit (MCID = 10.38%) and no benefit and could lead to different clinical decisions. Single study including only 104 patients.

e. The ends of the 95% confidence interval include appreciable clinical benefit (MCID = 0.23 L) and no benefit and could lead to different clinical decisions. Results from single study including only 104 patients.

f. The two studies reported by Castro 2015 included a mixed population of patients with moderate and severe asthma.

g. The ends of the 95% confidence interval include appreciable benefit and harm and could lead to different clinical decisions.

h. Single study including only 106 patients.

i. I^2 = 54% (P=0.07) may represent moderate heterogeneity. However the point estimates from the 5 studies have the same direction of effect and 4 of 5 studies have overlapping 95% confidence intervals. For these reasons we have not rated down for inconsistency.

j. The ends of the 95% confidence interval include appreciable benefit and no benefit and could lead to different clinical decisions. This judgement was based on a arbitrary clinical decision threshold of 15% increase or decrease in absolute effect.

k. There was a high incidence of adverse events in both reslizumab and placebo groups. The apparent benefit from reslizumab might be explained by a reduction of asthma-related adverse events with the active drug.

l. High risk of selective outcome reporting bias because 5 studies have reported any adverse events but only 2 studies have reported drug-related adverse events.

m. There is considerable statistical heterogeneity (I^2= 83%, P = 0.01), the effect estimates point in different directions (one study suggests benefit and the other suggests harm) and the 95% confidence intervals show minimal overlap.

n. This judgement was based on a arbitrary clinical decision threshold of 15% increase or decrease in absolute effect.

o.This judgement was based on a arbitrary clinical decision threshold of 10% increase or decrease in absolute effect.

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4. 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: 1125-1132.

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GRADE Evidence Profile: BENRALIZUMAB

Bibliography: Bleecker 2016, Castro 2014, FitzGerald 2016, Nair 2017, Park 2016

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Benralizumab	placebo	Relative (95% CI)	Absolute (95% CI)		
Quality of life (change from baseline) (follow up: range 28 weeks to 56 weeks; assessed with: Asthma Quality of Life Questionnaire (AQLQ); Scale from: 1 to 7; higher values indicate better quality of life; MCID 0.5)												
4 [1,2,3,4]	randomised trials	not serious	not serious	serious [a]	not serious	none	592	657	-	MD **0.32 higher** (0.19 higher to 0.45 higher)	⊕⊕⊕◯ MODERATE	CRITICAL
Quality of life (change from baseline) (follow up: 28 weeks; assessed with: Asthma Quality of Life Questionnaire (AQLQ); Scale from: 1 to 7; higher values indicate better quality of life; MCID 0.5) **<u>Study participants meet criteria for the diagnosis of severe asthma defined by the ERS/ATS Guidelines on Severe Asthma</u>[7]**												
1 [1]	randomised trials	not serious	not serious	not serious	very serious [b]	none	72	75	-	MD **0.45 higher** (0.14 higher to 0.76 higher)	⊕⊕◯◯ LOW	IMPORTANT
Asthma control (change from baseline) (follow up: range 28 weeks to 56 weeks; assessed with: Asthma Control Questionnaire (ACQ-6); Scale from: 0 to 6; lower values indicate better asthma control; MCID 0.5)												
4 [1,2,3,4]	randomised trials	not serious	not serious	serious [a]	not serious	none	870	946	-	MD **0.29 lower** (0.40 lower to 0.17 lower)	⊕⊕⊕◯ MODERATE	CRITICAL
Asthma control (change from baseline) (follow up: 28 weeks; assessed with: Asthma Control Questionnaire (ACQ-6); Scale from: 0 to 6; lower values indicate better asthma control; MCID 0.5) **<u>Study participants meet criteria for the diagnosis of severe asthma defined by the ERS/ATS Guidelines on Severe Asthma</u>[7]**												
1 [1]	randomised trials	not serious	not serious	not serious	very serious [b]	none	73	74	-	MD **0.55 lower** (0.86 lower to 0.24 lower)	⊕⊕◯◯ LOW	CRITICAL
Asthma symptoms (change from baseline) (follow up: range 28 weeks to 56 weeks; assessed with: different symptom scores; lower scores indicate less frequent and/or severe symptoms)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Benralizumab**	**placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
4 [1,2,3,4]	randomised trials	not serious	not serious	serious [a]	not serious	none	858	953	-	SMD **0.19 lower** (0.28 lower to 0.09 lower)	⊕⊕⊕◯ MODERATE	CRITICAL
Asthma symptoms (change from baseline) (follow up: 28 weeks; assessed with: Total asthma symptom score; lower scores indicate less frequent and/or severe symptoms) **Study participants meet criteria for the diagnosis of severe asthma defined by the ERS/ATS Guidelines on Severe Asthma [7]**												
1 [1]	randomised trials	not serious	not serious	not serious	very serious [c]	none	68	67	-	MD **0.18 lower** (0.52 lower to 0.16 higher)	⊕⊕◯◯ LOW	CRITICAL
Lung function (FEV1 % of predicted) (follow up: 52 weeks; MCID 10.38% [6])												
1 [5]	randomised trials	not serious	not serious	serious [d]	very serious [e]	none	25	26	-	MD **5.3 lower** (17.63 lower to 7.03 higher)	⊕◯◯◯ VERY LOW	IMPORTANT
Lung function (Pre-bronchodilator FEV1 litres, change from baseline) (follow up: range 28 weeks to 56 weeks; MCID 0.23 litre [6])												
4 [1,2,3,4]	randomised trials	not serious	not serious	serious [a]	not serious	none	879	982	-	MD **0.11 higher** (0.06 higher to 0.16 higher)	⊕⊕⊕◯ MODERATE	IMPORTANT
Lung function (Pre-bronchodilator FEV1 litres, change from baseline) (follow up: 28 weeks; MCID 0.23 litre [6]) **Study participants meet criteria for the diagnosis of severe asthma defined by the ERS/ATS Guidelines on Severe Asthma [7]**												
1 [1]	randomised trials	not serious	not serious	not serious	very serious [f]	none	69	73	-	MD **0.11 higher** (0.03 lower to 0.26 higher)	⊕⊕◯◯ LOW	IMPORTANT
Lung function(Post-bronchodilator FEV1 litres, change from baseline) (follow up: range 48 weeks to 56 weeks; MCID 0.23 litre [6])												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Benralizumab**	**placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
2 [2,4]	randomised trials	not serious	not serious	serious [g]	not serious	none	472	484	-	MD **0.1 higher** (0.04 higher to 0.16 higher)	⊕⊕⊕◯ MODERATE	IMPORTANT
Exacerbations (patients with ≥1 exacerbation) (follow up: range 28 weeks to 56 weeks)												
2 [1,2]	randomised trials	not serious	serious [h]	serious [i]	serious [j]	none	112/312 (35.9%)	165/323 (51.1%)	**RR 0.62** (0.36 to 1.06)	**194 fewer per 1,000** (from 327 fewer to 31 more)	⊕◯◯◯ VERY LOW	CRITICAL
Exacerbations (patients with ≥1 exacerbation) (follow up: 28 weeks) **Study participants meet criteria for the diagnosis of severe asthma defined by the ERS/ATS Guidelines on Severe Asthma[7]**												
1 [1]	randomised trials	not serious	not serious	not serious	serious [k]	none	17/73 (23.3%)	39/75 (52.0%)	**RR 0.45** (0.28 to 0.72)	**286 fewer per 1,000** (from 374 fewer to 146 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Rate of any exacerbation (Age range 12-75 years; follow up: range 28 weeks to 56 weeks)												
4 [1,2,3,4]	randomised trials	not serious	not serious	serious [a]	not serious	none	905	935	**Rate ratio 0.58** (0.47 to 0.73)	Incidence rate (events/patient/year): benralizumab 0.64; placebo 1.19	⊕⊕⊕◯ MODERATE	CRITICAL
Rate of any exacerbation (Age range 12-17 years; follow up: range 48 weeks to 56 weeks)												
2 [2,4]	randomised trials	not serious	not serious	serious [g]	very serious [j,l]	none	16	19	**Rate ratio 1.70** (0.50 to 5.81)	NA	⊕◯◯◯ VERY LOW	CRITICAL
Rate of any exacerbation (follow up: 28 weeks) **Study participants meet criteria for the diagnosis of severe asthma defined by the ERS/ATS Guidelines on Severe Asthma[7]**												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Benralizumab**	**placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
1 [1]	randomised trials	not serious	not serious	not serious	serious [k]	none	73	75	**Rate ratio 0.30** (0.17 to 0.53)	Incidence rate (events/patient/year): benralizumab 0.54; placebo 1.83	⊕⊕⊕◯ MODERATE	CRITICAL
Time to first asthma exacerbation (follow up: range 28 weeks to 56 weeks)												
3 [1,2,4]	randomised trials	not serious	not serious	serious [g]	not serious	none	579	590	**HR 0.57** (0.40 to 0.81)	-	⊕⊕⊕◯ MODERATE	CRITICAL
Time to first asthma exacerbation (follow up: 28 weeks) **Study participants meet criteria for the diagnosis of severe asthma defined by the ERS/ATS Guidelines on Severe Asthma[7]**												
1 [1]	randomised trials	not serious	not serious	not serious	serious [k]	none	73	75	**HR 0.32** (0.18 to 0.57)	-	⊕⊕⊕◯ MODERATE	CRITICAL
Rate of exacerbations requiring emergency department visit or hospitalisation (follow up: range 28 weeks to 56 weeks)												
3 [1,2,4]	randomised trials	not serious	serious [m]	serious [g]	serious [j]	none	579	590	**Rate ratio 0.45** (0.14 to 1.47)	Incidence rate (events/patient/year): benralizumab 0.04; placebo 0.18	⊕◯◯◯ VERY LOW	CRITICAL
Rate of exacerbations requiring emergency department visit or hospitalisation (follow up: 28 weeks) **Study participants meet criteria for the diagnosis of severe asthma defined by the ERS/ATS Guidelines on Severe Asthma[7]**												
1 [1]	randomised trials	not serious	not serious	not serious	serious [k]	none	73	75	**Rate ratio 0.07** (0.01 to 0.63)	Incidence rate (events/patient/year): benralizumab 0.02; placebo 0.32	⊕⊕⊕◯ MODERATE	CRITICAL
Exacerbations requiring emergency department visit or hospitalisation (patients with ≥1 exacerbation) (follow up: 56 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Benralizumab**	**placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
1 [2]	randomised trials	not serious	not serious	serious [n]	serious [j]	none	20/239 (8.4%)	20/248 (8.1%)	**RR 1.04** (0.57 to 1.88)	**3 more per 1,000** (from 35 fewer to 71 more)	⊕⊕◯◯ LOW	CRITICAL
Adverse events (follow up: range 28 weeks to 68 weeks)												
5 [1,2,3,4,5]	randomised trials	not serious	not serious	serious [o]	not serious [p]	none	737/1001 (73.6%)	883/1169 (75.5%)	**RR 0.96** (0.91 to 1.01)[q]	**30 fewer per 1,000** (from 68 fewer to 8 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Adverse events (follow up: 28 weeks) **Study participants meet criteria for the diagnosis of severe asthma defined by the ERS/ATS Guidelines on Severe Asthma[7]**												
1 [1]	randomised trials	not serious	not serious	not serious	very serious [k,r]	none	55/73 (75.3%)	62/75 (82.7%)	**RR 0.91** (0.77 to 1.08)[q]	**74 fewer per 1,000** (from 190 fewer to 66 more)	⊕⊕◯◯ LOW	CRITICAL
Drug-related adverse events (follow up: 48 weeks)												
1 [4]	randomised trials	serious [s]	not serious	serious [d]	not serious [p]	none	47/354 (13.3%)	34/370 (9.2%)	**RR 1.44** (0.95 to 2.19)	**40 more per 1,000** (from 5 fewer to 109 more)	⊕⊕◯◯ LOW	CRITICAL
Serious adverse events (follow up: range 28 weeks to 68 weeks)												
5 [1,2,3,4,5]	randomised trials	not serious	not serious	serious [o]	not serious [t]	none	109/1001 (10.9%)	157/1169 (13.4%)	**RR 0.79** (0.63 to 1.00)	**28 fewer per 1,000** (from 50 fewer to 0 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Serious adverse events (follow up: 28 weeks) **Study participants meet criteria for the diagnosis of severe asthma defined by the ERS/ATS Guidelines on Severe Asthma[7]**												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Benralizumab**	**placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
1 [1]	randomised trials	not serious	not serious	not serious	very serious [k,u]	none	7/73 (9.6%)	14/75 (18.7%)	**RR 0.51** (0.22 to 1.20)	**91 fewer per 1,000** (from 146 fewer to 37 more)	⊕⊕◯◯ LOW	CRITICAL
Systemic steroids (absolute final dose) (follow up: 28 weeks) **<u>Study participants meet criteria for the diagnosis of severe asthma defined by the ERS/ATS Guidelines on Severe Asthma[7]</u>**												
1 [1]	randomised trials	not serious	not serious	not serious	serious [k]	none	The median oral prednisone or prednisolone dose (range) at the final visit (week 28) was 10.0 mg/day (0.0 to 40.0) in patients who received placebo (n=75) and 5.0 mg/day (0.0 to 30.0) in patients who received benralizumab (n=73) . No statistical test comparing results from the two groups has been reported.				⊕⊕⊕◯ MODERATE	CRITICAL
Systemic steroids (percent reduction) (follow up: 28 weeks) **<u>Study participants meet criteria for the diagnosis of severe asthma defined by the ERS/ATS Guidelines on Severe Asthma[7]</u>**												
1 [1]	randomised trials	not serious	not serious	not serious	serious [k]	none	The median prednisone or prednisolone dose reduction from baseline (range) at the final visit (week 28) was 25.0% (–150% to 100%) in the placebo group (n=75) and 75.0% (–50% to 100%) in the benralizumab group (n=73) (Wilcoxon rank-sum test P<0.001). Negative values indicate an increase in the final oral prednisone or prednisolone dose from baseline.				⊕⊕⊕◯ MODERATE	CRITICAL
Loss of work or school days, Intensive care unit admission, Non-invasive ventilation, Intubation, Comorbidities, Upper airway symptoms - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	

CI: Confidence interval; **FEV1:** forced expiratory volume in 1 second; **MCID:** minimal clinically important difference; **MD:** Mean difference; **SMD:** Standardised mean difference; **RR:** Risk ratio; **HR:** Hazard Ratio; **NA:** Not acvailable

Explanations

a. Three studies (Bleecker 2016, Castro 2014 and FitzGerald 2016) included a mixed population of patients with moderate and severe asthma.

b. The ends of the 95% confidence interval include appreciable clinical benefit (MCID = 0.5) and no benefit and could lead to different clinical decisions. Results from single study with only 147 patients.

c. The end of the 95% confidence interval could lead to different clinical decisions. Results from single study including only 135 patients.

d. The study included a mixed population of patients with moderate and severe asthma.

e. The ends of the 95% confidence interval include appreciable clinical harm (MCID = 10.38%) and no benefit and could lead to different clinical decisions. Results from single study with only 51 patients.

f. The ends of the 95% confidence interval include appreciable clinical benefit (MCID = 0.23 ml) and no benefit and could lead to different clinical decisions. Results from single study with only 142 patients.

g. Two studies (Bleecker 2016 and FitzGerald 2016) included a mixed population of patients with moderate and severe asthma.

h. There is considerable statistical heterogeneity (I^2= 79%, P = 0.03) and the 95% confidence intervals show little overlap.

i. One study (Bleecker 2016) included a mixed population of patients with moderate and severe asthma.

j. The ends of the 95% confidence interval include appreciable clinical benefit and harm and could lead to opposite clinical decisions.

k. Single study including only 148 patients.

l. Two studies including only 35 patients aged 12-17 years.

m. There is considerable statistical heterogeneity (I^2= 82%, P = 0.004) and the point estimates from individual studies vary widely.

n. The study included a mixed population of patients with moderate and severe asthma

o. Four studies (Bleecker 2016, Castro 2014, FitzGerald 2016 and Park 2016) included a mixed population of patients with moderate and severe asthma.

p. This judgement was based on a arbitrary clinical decision threshold of 15% increase or decrease in absolute effect.

q. There was a high incidence of adverse events in both benralizumab and placebo groups. The apparent benefit from benralizumab might be explained by a reduction of asthma-related adverse events with the active drug.

r.The ends of the 95% confidence interval include appreciable clinical benefit and no benefit, assuming an arbitrary clinical decision threshold of 15% increase or decrease in absolute effect. This could lead to different clinical decisions.

s. High risk of selective outcome reporting bias because 5 studies have reported any adverse events but only 1 study has reported drug-related adverse events.

t. This judgement was based on a arbitrary clinical decision threshold of 10% increase or decrease in absolute effect.

u. The ends of the 95% confidence interval include appreciable clinical benefit and no benefit, assuming an arbitrary clinical decision threshold of 10% increase or decrease in absolute effect. This could lead to different clinical decisions.

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Evidence to Decision Framework

Should an anti-interleukin 5 strategy versus no anti-interleukin 5 strategy be used for adults and children with severe asthma?

POPULATION:	Adults and children with severe asthma
INTERVENTION:	Anti-interleukin 5 strategy (monoclonal antibodies directed against the interleukin 5 or its receptor)
COMPARISON:	No anti-interleukin 5 strategy
MAIN OUTCOMES:	Rate of exacerbations Time to first asthma exacerbation Asthma exacerbations requiring ER visits or hospitalization Lung function Asthma control Maintenance corticosteroid dose reduction Adverse events Serious adverse events Quality of life

BACKGROUND:

By definition, patients with severe asthma have disease that is either unresponsive to traditional therapies with inhaled corticosteroids and bronchodilators or require these therapies to maintain adequate control. To address this unmet need for improved therapies, several biologic therapies have been designed to target the inflammatory signature typical of most patients with asthma. Interleukin 5 (IL5) is the principal cytokine driving eosinophilic inflammation in most of these patients. Monoclonal antibodies that target the IL5 cytokine or its receptor have been found to be efficacious in randomized controlled trials in improving asthma-related outcomes. These three drugs in this category are mepolizumab, reslizumab, and benralizumab, and will henceforth be referred to as the anti-IL5 strategy. This systematic review and meta-analysis synthetizes the data from randomized controlled trials and meta-analyses investigating the anti-IL5 strategy and provides treatment recommendations based on the results.

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○Don't know	Asthma exacerbations are a critically important outcome for the patients with asthma who experience these and the clinicians who care for them. Relative to participants assigned to placebo, those assigned to mepolizumab experienced a 50% reduction (95% CI 39-65%) (see evidence profiles) in their rates of asthma exacerbations; participants assigned to reslizumab and benralizumab demonstrated similar reductions in rates of asthma exacerbations [54% (95% CI 42-63%) and 42% (95% CI 27-53%), respectively]. Although a defined threshold for clinically meaningful reductions in asthma exacerbations has not been universally agreed upon, the effect sizes in reductions in asthma exacerbations for these three drugs are considered clinically substantial by most practitioners. Among adolescent participants (ages 12-17 years, n=35 between two trials), those assigned to benralizumab experienced a 1.7x increase (95% CI 0.50x-5.81x) in their rates of asthma exacerbations (very low quality evidence). Another critically important outcome in asthma includes asthma symptom scores. Although the evidence favors all anti-IL5 strategy drugs relative to placebo on these outcomes, their relative change was not as large compared to the improvement observed with asthma exacerbations. Relative to participants assigned to placebo, those assigned to mepolizumab experienced a 0.43-point decrease (i.e. improvement) in Asthma Control Questionnaire (ACQ) (95% CI 0.31-0.56-point decrease); participants assigned to reslizumab and benralizumab demonstrated similar improvements in ACQ scores [0.26 (95% CI 0.18-0.33-point decrease) and 0.29 (95% CI 0.17-0.40 point decreases), respectively]. Although these were statistically significant decreases in ACQ scores, on average these drugs did not surpass the 0.5-point decrease threshold traditionally assigned as the MCID in ACQ symptom score for trials in asthma. Meta-analytical results on other outcomes appear in the online supplement.	• The decision to consider changes in lung function [forced expiratory volume in the first second (FEV1)] as 'important' outcomes as opposed to 'critical' outcomes is due to their place relative to other critical outcomes. We understand that most clinicians would prescribe anti-IL5 strategy drugs due to their efficacy in reducing asthma exacerbations despite only modest improvements in lung function. • Data from children or adolescents are unavailable for mepolizumab and reslizumab. There are data available on the effects of benralizumab on adolescents with severe asthma, but this subset of the cohort is small. The resulting confidence intervals around effect estimates are large, which makes the quality of the data for adolescents very low. As noted in the FDA approval statement, the decision to allow the use of benralizumab in adolescents was based on the impracticality of conducting a sufficiently powered study among severe asthmatic adolescents due to the low prevalence of this population; the similarities in pharmacokinetic and pharmacodynamic values for this drug, and the absence of major safety concerns for the population. More data are needed in order to have greater quality recommendations for adolescents. • The meta-analysis for mepolizumab included only the trials that tested the FDA- and EMA-approved dose of 100mg administered subcutaneously. • Taken together, however, the reduction in asthma exacerbations is substantial enough for this committee to judge the desirable effects of an anti-IL5 strategy as large, regardless of relatively smaller effects on lung function and symptom scores.

UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	In the RCTs analysed, the risk of a study participant developing either an adverse event or a serious adverse event was lower for those participants assigned to any of the 3 anti-IL5 strategy drugs compared to those assigned to placebo. Relative to placebo, the risk of developing an adverse event for a participant assigned to mepolizumab was 7% lower (95% CI 1-12% lower) and for those assigned to reslizumab it was 12% lower (95% CI 4-18% lower). This difference was not statistically significant for those assigned to benralizumab, but the direction of the effect was also toward a lower risk of adverse events (3% lower). Similarly, participants experienced a lower risk of serious adverse events (not statistically significant) when assigned to anti-IL5 strategy drugs. The lower risk of *total* adverse events is likely driven by the reduction in asthma exacerbations shown by these drugs. Data are available on *drug-related* adverse events from all 3 mepolizumab trials, but only from 2 of 5 reslizumab trials and 1 of 5 benralizumab trials. These data show that, relative to placebo, participants assigned to mepolizumab had a 35% greater relative risk of drug-related adverse events (95% CI 1-81% greater RR); those assigned to reslizumab had a 22% lower relative risk and those assigned to benralizumab had a 44% greater relative risk, however the effect for last two drugs was not statistically significant.	Research evidence reveals that the rates of adverse events with anti-IL5 therapies are not substantially different from placebo. Infrequent but severe adverse reactions, including hypersensitive reactions, can not be excluded since randomised clinical trials are not powered enough to detect them. Safety data from phase 3 extension studies have been recently published and are reassuring. Post-authorisation phamacovigilance systems, including larger cohorts of patients receiving these treatments, are expected to provide additional real-life safety data.
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ● Very low ● Low ● Moderate ○ High ○ No included studies	Mepolizumab (population meets the definition of severe asthma defined by the ERS/ATS Guidelines): moderate quality of evidence. Benralizumab: --overall population (patients with moderate and severe persistent asthma): very low quality of evidence; --population that meets criteria for the diagnosis of severe asthma defined by the ERS/ATS Guidelines: low quality of evidence Reslizumab: --overall population (patients with moderate and severe persistent asthma):low quality of evidence; --population that meets criteria for the diagnosis of severe asthma defined by the ERS/ATS Guidelines: low quality of evidence	Our certainty assessment relies on study design (randomized controlled trials), risk of bias, inconsistency, indirectness , and imprecision . Further the certainty is based on the quality of evidence that is lowest among critical outcomes. The RCTs on all anti-IL5 strategy drugs were mainly designed to investigate changes in asthma exacerbations. Consequently, the certainty of the data for this critical outcome is high (mepolizumab and reslizumab) or moderate (benralizumab). However, the certainty of other outcomes such as respiratory symptoms was lower for all three drugs, and therefore downgraded the overall certainty of the evidence.

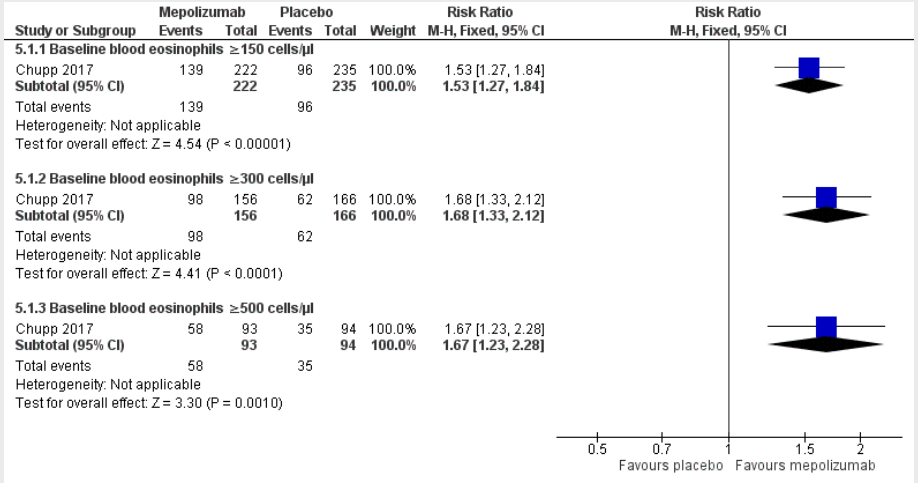
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability ○ No known undesirable outcomes	No evidence identified.	There is no important uncertainty about how patients and the clinicians who care for them assess asthma exacerbations. On the other hand, asthma exacerbations is not the only critical outcome for patients and clinicians, who also consider the effect of interventions on other outcomes, such as changes in lung function, change in maintenance dose of systemic corticosteroids, asthma symptoms, and quality of life. Although the effect size of anti-IL5 strategy drugs is not uniform across these outcomes, these drugs tended to improve to varying degrees all asthma related outcomes. For instance, although the reduction in asthma exacerbation rates is greater in magnitude than the change in lung function for all 3 of these drugs, all 3 did improve lung function. Further, patients and clinicians rarely decide to prescribe these drugs based on only one of these outcomes in isolation. All three anti-IL5 strategy drugs are currently FDA and EMA approved in patients with severe eosinophilic asthma. Patients with asthma of greater severity are more likely to experience a greater rate of asthma exacerbations. Therefore, the decision to whether or not to prescribe these drugs is currently restricted to patients for whom the main outcome researched in the anti-IL5 strategy trials—asthma exacerbations—is likely to be important. Further, many pharmacy formularies for physician groups and hospitals restrict these drugs to patients

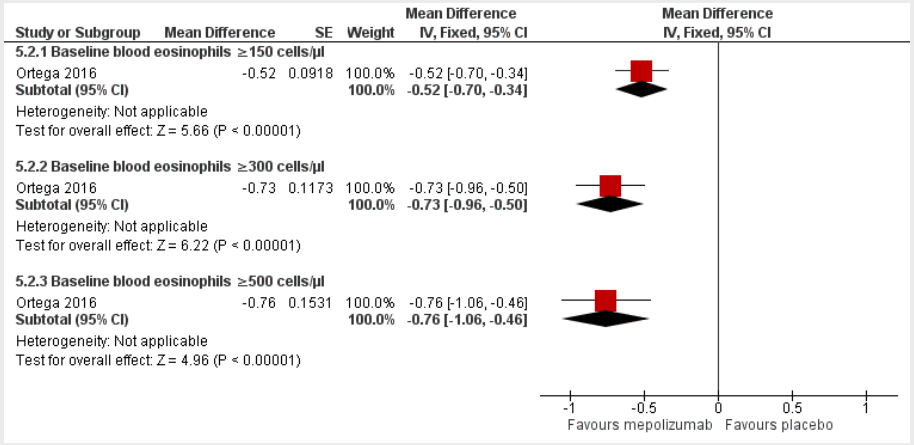
			with severe asthma and a recent history of asthma exacerbations.
BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ Don't know	All three anti-IL5 strategy drugs have been associated with large desirable effects and small undesirable effects.	As noted above, both serious and non-serious side effects were noted in clinical trials to have occurred more commonly in the placebo groups to which these drugs were compared. Thus, considering the substantial benefit in terms of reducing asthma exacerbations, the balance favors using an anti-IL5 strategy.
COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ● Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	The December 2018 report by the Institute for Clinical and Economic Review (ICER) states that anti-IL5 strategy drugs cost >$340,000 per quality-adjusted life years (QALY) gained when compared to standard of care (ICER 2018). These figures far exceed the accepted threshold for a cost-effective intervention of $150,000 per QALY gained.	Therefore, the alternative is favored over an anti-IL5 strategy from a cost-effectiveness standpoint.
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ○ Low ○ Moderate ● High ○ No included studies	The manufacturers' listed annual net prices are $29,500, $28,900, and $27,800 for mepolizumab, reslizumab, and benralizumab, respectively, after applying discounts and rebates (ICER 2018).	
EQUITY	**What would be the impact on health equity?** ○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased	No evidence identified.	In the US, racial and ethnic minorities, and individuals of lower socioeconomic status have been documented to have less access to specialty clinics and are less likely to use controller therapy for asthma. Since anti-IL5 strategy drugs are mainly prescribed by specialists it is likely

	○ Varies ○ Don't know		that racial and ethnic minorities will be less likely to be prescribed one of these drugs. Other groups may thus experience greater reductions in asthma exacerbations due to access to these drugs, which will thus reduce health equity. Similarly, patients with severe asthma who live in regions with fewer specialists will be less likely to receive these drugs, thus reducing equity between areas with high and low access to specialty care. On the other hand, the manufacturers of these drugs have programs in place to reduce patients' out of pocket costs for these drugs, which may partly mitigate the decrease in equity posed by differences in access by socioeconomic status and race/ethnicity.
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	No evidence identified.	Most patients with severe asthma welcome the possibility of relief from asthma through anti-IL5 strategy drugs. Health insurance companies and clinic administrations find anti-IL5 strategy drugs less acceptable due to their high cost.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	No evidence identified.	The feasibility to implement is limited by the prescription of these drugs only by asthma specialists with the clinical resources to administer these drugs and monitor patients. Clinicians also need to have access to a laboratory that can document peripheral blood eosinophils in these patients. Patients without access to such clinicians would find it very difficult to receive these drugs.

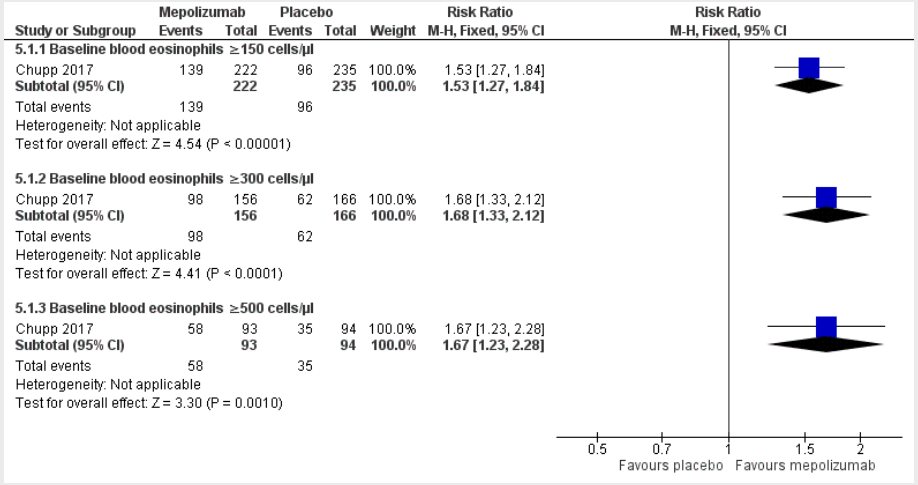
Should a measurement of a specific biomarker be used to guide initiation of treatment with a monoclonal anti-IL5 or IL5Rα antibody in adults and children with severe asthma? (biomarkers being exhaled NO, peripheral or sputum eosinophils, and serum periostin)

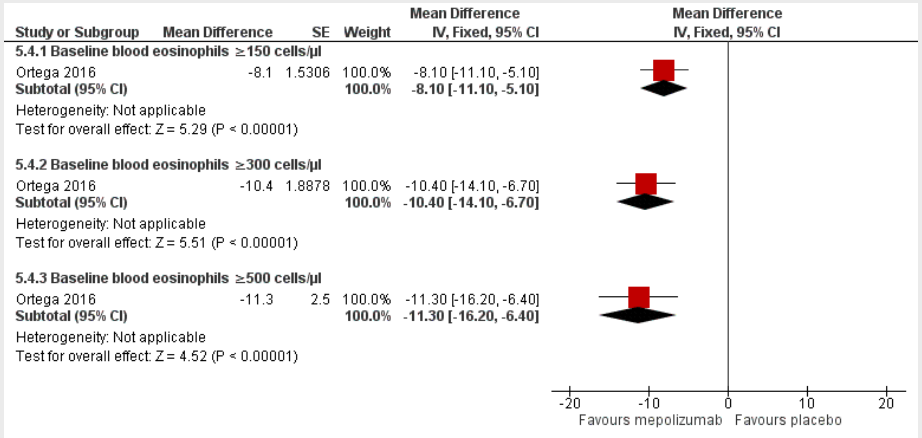
GRADE Evidence Profile: MEPOLIZUMAB (according to baseline number of blood eosinophils)

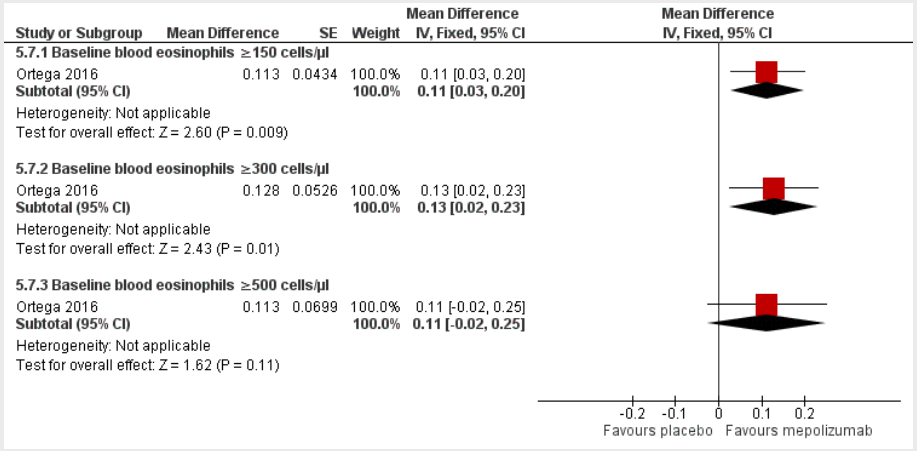
Outcome № of participants (studies)	Relative effect (95% CI)	**Anticipated absolute effects (95% CI)** **Difference**	Certainty	What happens
Asthma control (ACQ-5 responders defined as patients achieving a ≥0.5-point reduction from baseline in ACQ-5 score) assessed with: Asthma Control Questionnaire (ACQ-5); Scale from: 0 to 6; lower values indicate better asthma control; MCID 0.5. Follow up: 24 weeks № of participants: 457 (1 RCT) [1] Importance: CRITICAL	Percentage of patients treated with mepolizumab who achieved a ≥0.5-point reduction from baseline in ACQ-5 score compared to placebo were: Eosinophil ≥ 150/uL: 63% versus 41%, RR (95%CI) = 1.53 (1.27 to 1.84), Absolute effect = 217 more per 1,000 (from 110 more to 343 more), n=457. Eosinophil ≥ 300/uL: 63% versus 37%, RR (95%CI) = 1.68 (1.33 to 2.12), Absolute effect = 254 more per 1,000 (from 123 more to 418 more), n=322. Eosinophil ≥ 500/uL: 62% versus 37%, RR (95%CI) = 1.67 (1.23 to 2.28), Absolute effect = 249 more per 1,000 (from 86 more to 477 more), n=187.  	⊕⊕⊕◯ MODERATE b,c	There are significant increases in the number of patients treated with mepolizumab compared to placebo who achieve a reduction of at least 0.5 point in the ACQ-5 score. Increases are seen in patients with baseline blood eosinophil counts ≥150/uL, ≥300/uL and ≥500/uL. However there is appreciable overlap of the 95% CIs.

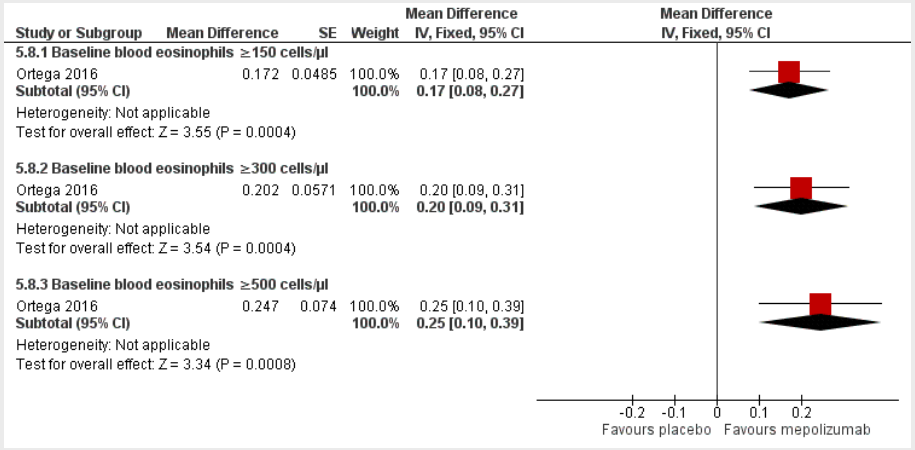
Outcome № of participants (studies)	Relative effect (95% CI)	**Anticipated absolute effects (95% CI)**			Certainty	What happens
				Difference		
Asthma control (change from baseline) assessed with: Asthma Control Questionnaire (ACQ-5); Scale from: 0 to 6; lower values indicate better asthma control; MCID 0.5. Follow up: 32 weeks № of participants: 402 (1 RCT) [2] Importance: CRITICAL	Mean change from baseline to week 32 in patients treated with mepolizumab compared to placebo were: Eosinophil ≥150/uL: Mean difference (95%CI) = -0.52 (-0.70 to -0.34), n=402. Eosinophil ≥300/uL: Mean difference (95%CI) = -0.73 (-0.96 to -0.50), n=274. Eosinophil ≥500/uL: Mean difference (95%CI) = -0.76 (-1.06 to -0.46), n=171.[d]  			⊕◯◯◯ VERY LOW b,c,e,f	There are significant improvements in asthma control assessed by the ACQ-5 in patients treated with mepolizumab compared to placebo at 32 weeks of follow up. Improvements are seen in patients with baseline blood eosinophil counts ≥150/uL, ≥300/uL and ≥500/uL. However the 95% CI of the subgroups ≥150 cells/uL and ≥500 cells/uL include a response below the MCID and there is appreciable overlap of the 95% CIs.

Outcome № of participants (studies)	Relative effect (95% CI)	**Anticipated absolute effects (95% CI)**			Certainty	What happens
				Difference		
Quality of life (SGRQ responders defined as patients achieving a ≥4-point reduction from baseline in SGRQ total score) assessed with: St George's Respiratory Questionnaire (SGRQ); Scale from: 0 to 100; higher scores indicate worse quality of life; MCID 4 units. Follow up: 24 weeks № of participants: 456 (1 RCT) [1] Importance: CRITICAL	Percentage of patients treated with mepolizumab who achieved a ≥ 4 point reduction from baseline in SGRQ total score compared to placebo were: Eosinophil ≥ 150/uL: 73% versus 55%, RR (95%CI) = 1.33 (1.16 to 1.53), Absolute effect = 182 more per 1,000 (from 88 more to 292 more), n=456. Eosinophil ≥ 300/uL: 73% versus 54%, RR (95%CI) = 1.35 (1.14 to 1.61), Absolute effect = 189 more per 1,000 (from 76 more to 329 more), n=321. Eosinophil ≥ 500/uL: 74% versus 57%, RR (95%CI) = 1.29 (1.05 to 1.60), Absolute effect = 167 more per 1,000 (from 29 more to 345 more), n=187.				⨁⨁⨁◯ MODERATE [b,c]	There are significant increases in the number of patients treated with mepolizumab compared to placebo who achieve a reduction of at least 4 points in the SGRQ total score. Increases are seen in patients with baseline blood eosinophil counts ≥150/uL, ≥300/uL and ≥500/uL. However there is appreciable overlap of the 95% CIs.

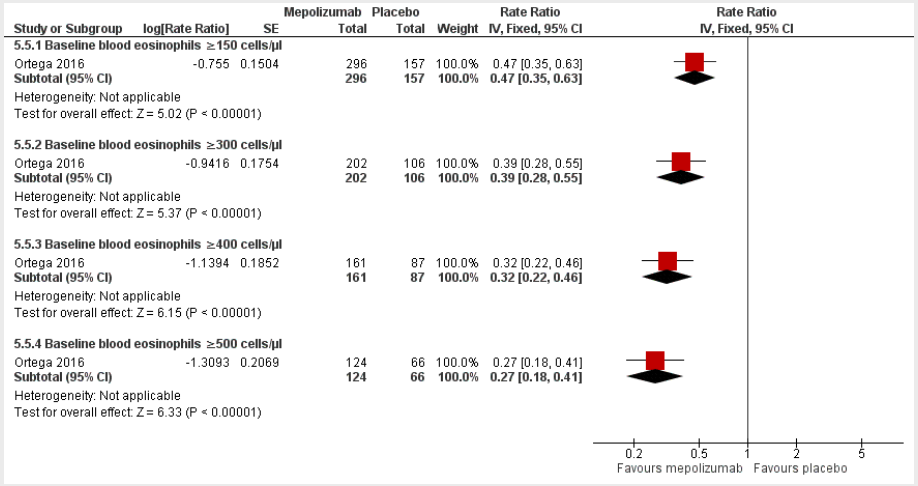


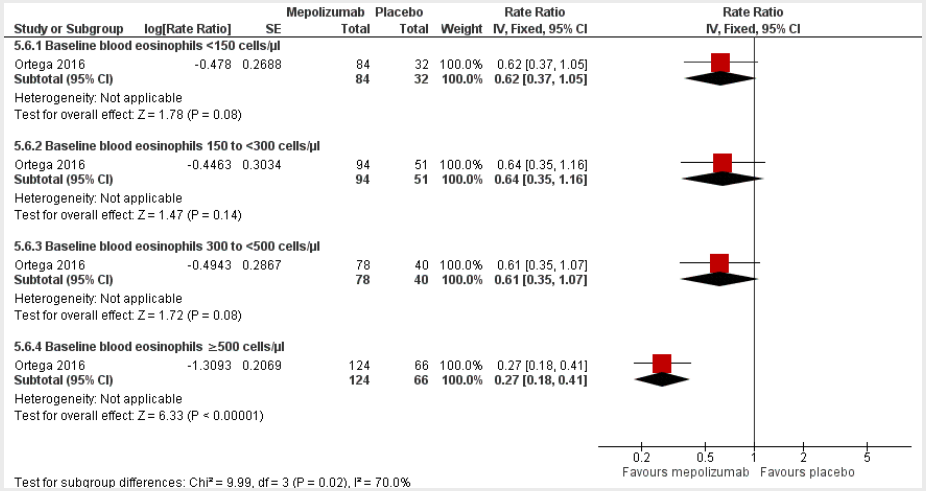
Outcome № of participants (studies)	Relative effect (95% CI)	**Anticipated absolute effects (95% CI)**			Certainty	What happens
				Difference		
Quality of life (change from baseline) assessed with: St George's Respiratory Questionnaire; Scale from: 0 to 100; higher scores indicate worse quality of life; MCID 4 units. Follow up: 32 weeks № of participants: 420 (1 RCT) [2] Importance: CRITICAL	Mean change from baseline to week 32 in patients treated with mepolizumab compared to placebo were: Eosinophil ≥150/uL: Mean difference (95%CI) = -8.10 (-11.10 to -5.10), n=420. Eosinophil ≥300/uL: Mean difference (95%CI) = -10.40 (-14.10 to -6.70), n=288. Eosinophil ≥500/uL: Mean difference (95%CI) = -11.30 (-16.20 to -6.40), n=179.[d]  	⨁⨁◯◯ LOW [b,c,e]	There are significant improvements in respiratory symptoms measured by the SGRQ in patients treated with mepolizumab compared to placebo at 32 weeks of follow up. Improvements are seen in patients with baseline blood eosinophil counts ≥150/uL, ≥300/uL and ≥500/uL, however there is appreciable overlap of the 95% CIs.

Outcome № of participants (studies)	Relative effect (95% CI)	**Anticipated absolute effects (95% CI)**			Certainty	What happens
				Difference		
Lung function (Pre-bronchodilator FEV1 litres, change from baseline); MCID 0.23 liter[4] follow up: 32 weeks № of participants: 423 (1 RCT) [2] Importance: IMPORTANT	Mean change from baseline to week 32 in patients treated with mepolizumab compared to placebo were: Eosinophil ≥150/uL: Mean difference (95%CI) = 0.11 L (0.03 L to 0.20 L), n=423. Eosinophil ≥300/uL: Mean difference (95%CI) = 0.13 L (0.02 L to 0.23 L), n=290. Eosinophil ≥500/uL: Mean difference (95%CI) = 0.11 L (-0.02 L to 0.25 L), n=181.[d]  	⨁◯◯◯ VERY LOW b,c,e,f	There is a significant change in pre-BD FEV1 (litres) with mepolizumab compared to placebo in the subgroups of patients with blood eosinophil counts ≥150/uL and ≥300/uL at 32 weeks of follow up, whereas there are no differences in similar terms for those patients with blood eosinophils ≥500/uL at the same follow up. There is appreciable overlap of the 95% CIs.

Outcome № of participants (studies)	Relative effect (95% CI)	**Anticipated absolute effects (95% CI)** **Difference**	Certainty	What happens
Lung function (Post-bronchodilator FEV1 litres, change from baseline); MCID 0.23 liter[4] follow up: 32 weeks № of participants: 386 (1 RCT) [2] Importance: IMPORTANT	Mean change from baseline to week 32 in patients treated with mepolizumab compared to placebo were: Eosinophil ≥150/uL: Mean difference (95%CI) = 0.17 L (0.08 L to 0.27 L), n=386. Eosinophil ≥300/uL: Mean difference (95%CI) = 0.20 L (0.09 L to 0.31 L), n=268. Eosinophil ≥500/uL: Mean difference (95%CI) = 0.25 L (0.10 L to 0.39 L), n=166.[d]  	⊕◯◯◯ VERY LOW b,c,e,f	There is a significant change in post-BD FEV1 (litres) with mepolizumab compared to placebo in the subgroups of patients with blood eosinophil counts ≥150/uL, ≥300/uL and ≥500/uL at 32 weeks of follow up. However there is appreciable overlap of the 95% CIs.

Outcome № of participants (studies)	Relative effect (95% CI)	**Anticipated absolute effects (95% CI)**			Certainty	What happens
				Difference		
Exacerbation rate (mean exacerbation rate per patient per year); lower rates, greater reduction in exacerbations; Follow up: 32 weeks № of participants: 453 (1 RCT) [2] Importance: CRITICAL	Annualised mean exacerbation rates per patient treated with mepolizumab compared to placebo were: Eosinophil ≥150/uL: 0.78 vs 1.65, Rate ratio (95%CI) = 0.47 (0.35 to 0.63), n=453. Eosinophil ≥300/uL: 0.78 vs 1.98, Rate ratio (95%CI) = 0.39 (0.28 to 0.55), n=308. Eosinophil ≥400/uL: 0.66 vs 2.06, Rate ratio (95%CI) = 0.32 (0.22 to 0.46), n=248. Eosinophil ≥500/uL: 0.58 vs 2.11, Rate ratio (95%CI) = 0.27 (0.18 to 0.41), n=190.				⨁⨁◯◯ LOW [b,c,e]	There is a significant reduction of exacerbation rates with mepolizumab compared to placebo in those patients with baseline blood eosinophil counts ≥150/uL, ≥300/uL, ≥400/uL and ≥500/uL. However there is overlap of the 95% CIs.



Outcome № of participants (studies)	Relative effect (95% CI)	**Anticipated absolute effects (95% CI)**			Certainty	What happens
				Difference		
Exacerbation rate (mean exacerbation rate per patient per year); lower rates, greater reduction in exacerbations; Follow up: 32 weeks № of participants: 569 (1 RCT) [2] Importance: CRITICAL	Annualised mean exacerbation rates per patient treated with mepolizumab compared to placebo were: Eosinophil <150/uL: 1.19 vs 1.92, Rate ratio (95%CI) = 0.62 (0.37 to 1.05), n=116. Eosinophil 150 to <300/uL: 0.66 vs 1.02, Rate ratio (95%CI) = 0.64 (0.35 to 1.16), n=145. Eosinophil 300 to <500/uL: 1.01 vs 1.66, Rate ratio (95%CI) = 0.61 (0.35 to 1.07), n=118. Eosinophil ≥500/uL: 0.58 vs 2.11, Rate ratio (95%CI) = 0.27 (0.18 to 0.41), n=190. Test for subgroup differences, p=0.02.  	⊕⊕◯◯ LOW [b,c,e]	There is a significant reduction of exacerbation rates with mepolizumab compared to placebo in those patients with baseline blood eosinophil counts ≥500/uL, but not in patients with eosinophil counts <150/uL, 150 to <300/uL and 300 to <500/uL. There are statistically significant differences between subgroups.

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference; **OR:** Odds ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. The participants included in these analyses have been considered to represent a population of severe asthmatics as defined by the ERS/ATS Guidelines on Severe Asthma 2014[3].

b. Potential risk of bias associated with selective outcome reporting bias (non-predefined post-hoc analyses).

c. The inclusion criteria for participants 12-17 years of age required treatment with inhaled corticosteroids at a lower dose than that recommended by the ERS/ATS Guidelines on Severe Asthma (2014)[3]. The proportion of included participants 12-17 years of age was not specified. However we have assumed the proportion of included participants 12-17 years was small relative to the whole study population and therefore we have not downgraded for indirectness.

d. The measure of effect was not clearly specified in Ortega 2016, but we have assumed it was presented as mean difference between change-from-baseline measures.

e. Mepolizumab doses (100 mg SC and 75 mg IV) were combined for the analysis, as reported by Ortega 2016.

f. The ends of the 95% confidence interval of at least one subgroup include appreciable benefit and no benefit and could lead to different clinical decisions.

References

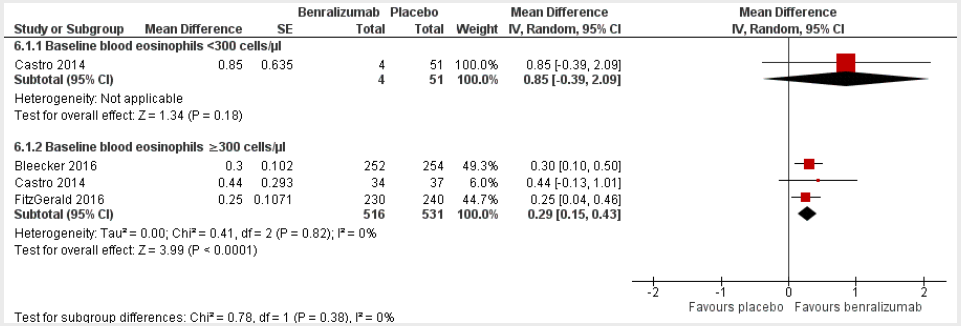
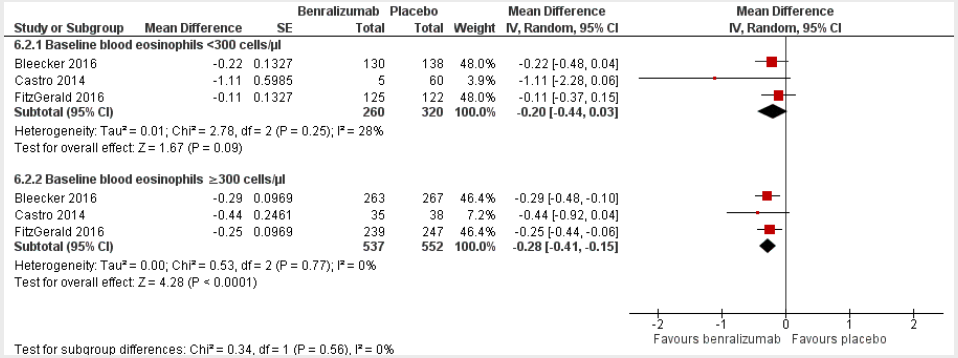
1. Chupp GL, Bradford ES, Albers FC, et al. Efficacy of mepolizumab add-on therapy on health-related quality of life and markers of asthma control in severe eosinophilic asthma (MUSCA): a randomised, double-blind, placebo-controlled, parallel-group, multicentre, phase 3b trial. Lancet Respir Med 2017; 5: 390–400.

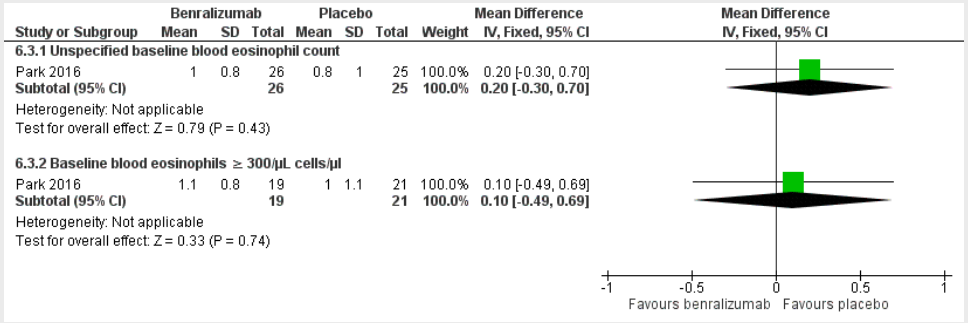
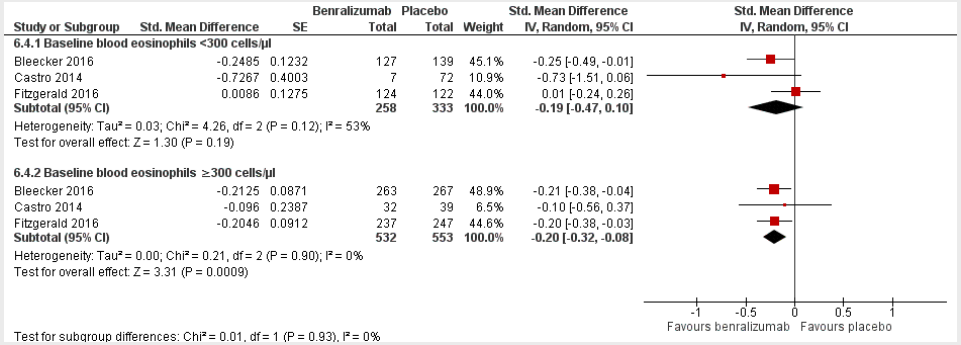
2. Ortega HG, Yancey SW, Mayer B, et al . Severe eosinophilic asthma treated with mepolizumab stratified by baseline eosinophil thresholds: a secondary analysis of the DREAM and MENSA studies. Lancet Respir Med 2016; 4: 549-556.

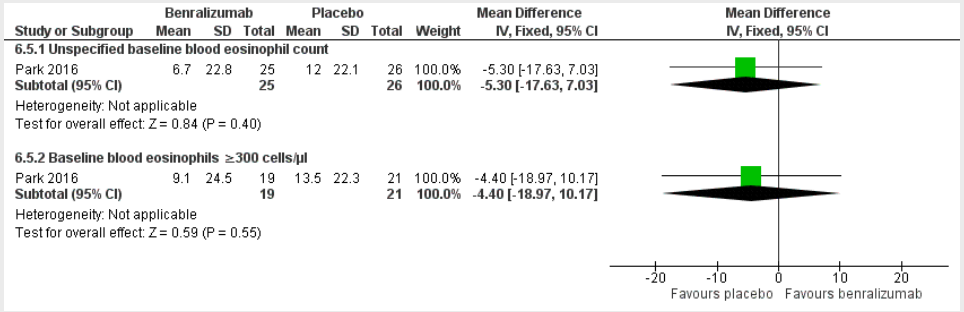
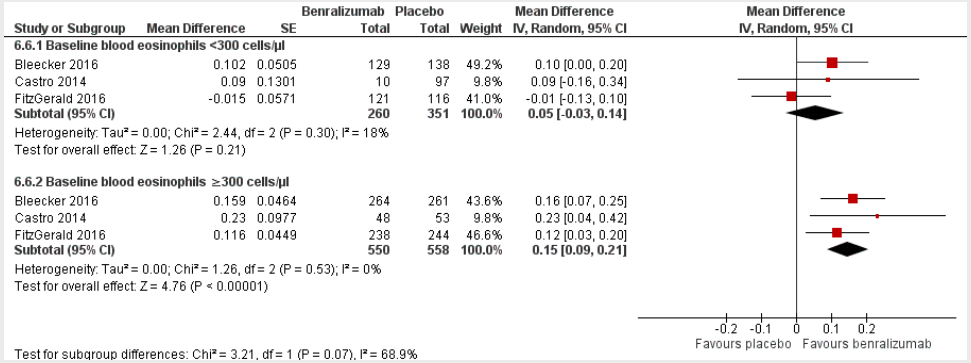
3. Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J 2014; 43: 343-373.

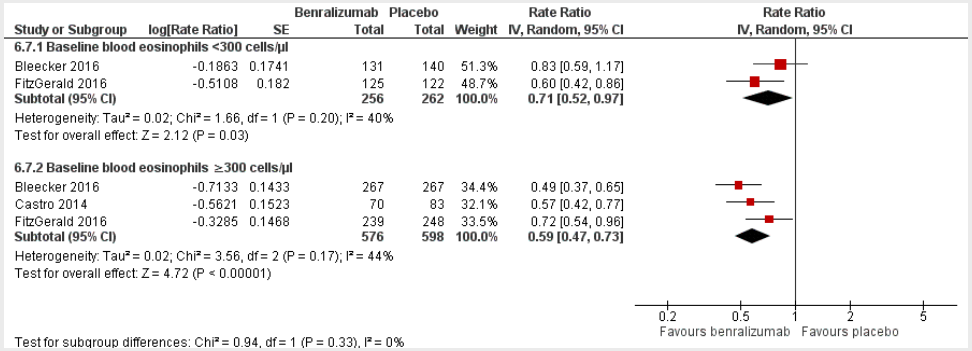
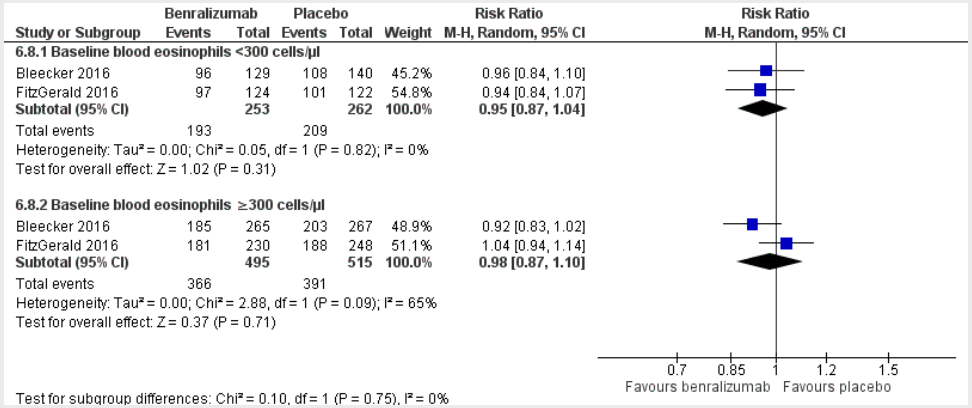
4. Santanello NC, Zhang J, Seidenberg B, Reiss TF, Barber BL. What are minimal important changes for asthma measures in a clinical trial? Eur Respir J1999; 14: 23-27.

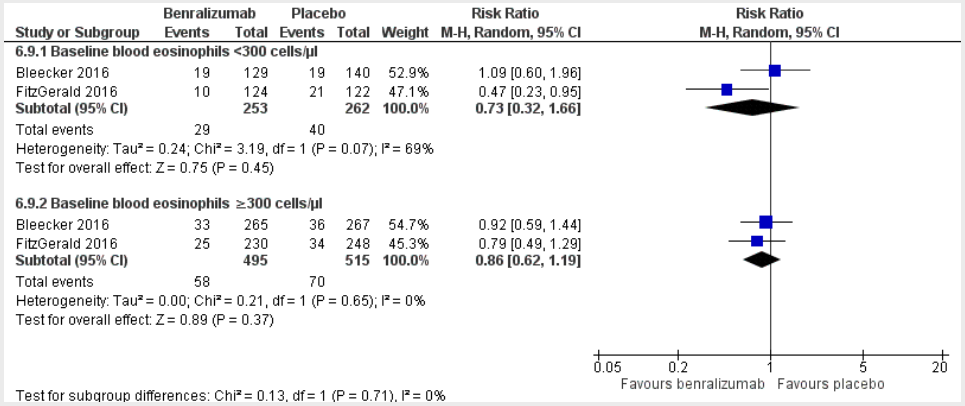
GRADE Evidence Profile: BENRALIZUMAB (according to baseline number of blood eosinophils)

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI) Difference	Certainty	What happens
Quality of life (change from baseline) assessed with: Asthma Quality of Life Questionnaire (AQLQ) follow up: range 28 weeks to 56 weeks; Scale from: 1 to 7; higher values indicate better quality of life; MCID 0.5) № of participants: 1194 (3 RCTs) [1,2,3] Importance: CRITICAL	Mean change from baseline in AQLQ score in patients treated with benralizumab compared to placebo were: Eosinophil <300/µL: Mean difference (95% CI) = 0.85 (-0.39 to 2.09), n=55 ; Eosinophil ≥300/µL: Mean difference (95% CI) = 0.29 (0.15 to 0.43), n=1047 . Test for subgroup differences, p=0.38.  	⊕◯◯◯ VERY LOW [a,b,c]	There are significant improvements in asthma quality of life assessed by the AQLQ with benralizumab compared to placebo in patients with baseline blood eosinophil counts ≥300/µL but not <300/µL. There are no statistically significant differences between subgroups.
Asthma control (change from baseline) assessed with: Asthma Control Questionnaire (ACQ-6) follow up: range 28 weeks to 56 weeks Scale from: 0 to 6; lower values indicate better asthma control; MCID 0.5 № of participants: 1236 (3 RCTs) [1,2,3] Importance: CRITICAL	Mean change from baseline in ACQ-6 score in patients treated with benralizumab compared to placebo were: Eosinophil <300/µL: Mean difference (95% CI) = -0.20 (-0.44 to 0.03), n=580; Eosinophil ≥300/µL: Mean difference (95% CI) = -0.28 (-0.41 to -0.15), n=1089. Test for subgroup differences, p=0.56.  	⊕⊕◯◯ LOW [b,d]	There are significant improvements in asthma control assessed by the ACQ-6 with benralizumab compared to placebo in patients with baseline blood eosinophil counts ≥300/µL but not <300/µL. There are no statistically significant differences between subgroups.

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI) Difference	Certainty	What happens
Asthma control (at week 52) assessed with: Asthma Control Questionnaire (ACQ-6); Scale from: 0 to 6; lower values indicate better asthma control; MCID 0.5 follow up: 52 weeks; № of participants: 51 (1 RCT) [4] Importance: CRITICAL	Mean ACQ-6 score at week 52 in patients treated with benralizumab compared to placebo were: Unspecified blood eosinophil count: Mean difference (95% CI) = 0.20 (-0.30 to 0.70), n=51; Eosinophil ≥300/µL: Mean difference (95% CI) = 0.10 (-0.49 to 0.69), n=40.  	⊕◯◯◯ VERY LOW [e,f]	There are no significant improvements in asthma control assessed by the ACQ-6 with benralizumab compared to placebo in patients with baseline blood eosinophil counts ≥300/µL or with unspecified eosinophil counts at 52 weeks of follow up. There is appreciable overlap of the 95% CIs.
Asthma symptoms (change from baseline) assessed with: different symptom scores; lower scores indicate less frequent and/or severe symptoms; follow up: range 28 weeks to 56 weeks № of participants: 1220 (3 RCTs) [1,2,3] Importance: CRITICAL	Mean change from baseline in asthma symptom scores in patients treated with benralizumab compared to placebo were: Eosinophil <300/µL: standardized mean difference (95% CI) = -0.19 (-0.47 to 0.10), n=591; Eosinophil ≥300/µL: standardized mean difference (95% CI) = -0.20 (-0.32 to -0.08), n=1085. Test for subgroup differences, p=0.93.  	⊕◯◯◯ VERY LOW [b,g,h]	There are significant improvements in asthma symptoms with benralizumab compared to placebo in those patients with baseline blood eosinophil counts ≥300/µL but not <300/µL. There are no statistically significant differences between subgroups.

Outcome № of participants (studies)	Relative effect (95% CI)	**Anticipated absolute effects (95% CI)** **Difference**	Certainty	What happens
Lung function (FEV1% of predicted)[i] follow up: 52 weeks MCID 10.38% [6] № of participants: 40 (1 RCT) [4] Importance: IMPORTANT	Mean FEV1% of predicted at week 52 in patients treated with benralizumab compared to placebo were: Unspecified blood eosinophil count: Mean difference (95% CI) = -5.30% (-17.63 to 7.03%), n=51; Eosinophil ≥300/µL: Mean difference (95% CI) = -4.40% (-18.97 to 10.17%), n=40.  	⊕◯◯◯ VERY LOW [e,j]	There are no significant changes in FEV1% of predicted with benralizumab compared to placebo in patients with baseline blood eosinophil counts ≥300/µL or with unspecified eosinophil counts at 52 weeks of follow up. There is appreciable overlap of the 95% CIs.
Lung function (Pre-bronchodilator FEV1 litres) follow up: range 28 to 56 weeks; MCID 0.23 litre[6] № of participants: 611 (3 RCTs) [1,2,3] Importance: IMPORTANT	Mean change from baseline in pre-bronchodilator FEV1 (litres) in patients treated with benralizumab compared to placebo were: Eosinophil <300/µL: Mean difference (95% CI) = 0.05 L (-0.03 to 0.14 L), n=611; Eosinophil ≥300/µL: Mean difference (95% CI) = 0.15 L (0.09 to 0.21 L), n=1108. Test for subgroup differences, p=0.07.  	⊕⊕◯◯ LOW [b,g]	There is a significant increase in pre-BD FEV1 (litres) with benralizumab compared to placebo in the subgroup of patients with blood eosinophil counts ≥300/uL, whereas there are no differences for those patients with blood eosinophils <300/uL. However there are no statistically significant differences between subgroups.

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI) Difference	Certainty	What happens
Rate of any exacerbation follow up: range 28 weeks to 56 weeks № of participants: 1322 (3 RCTs) [1,2,3] Importance: CRITICAL	Annualised mean exacerbation rates per patient treated with mepolizumab compared to placebo were: Eosinophil <300/uL: Rate ratio (95%CI) = 0.71 (0.52 to 0.97), n=518. Eosinophil ≥300/uL: Rate ratio (95%CI) = 0.59 (0.47 to 0.73), n=1174. Test for subgroup differences, p=0.33.  	⊕⊕◯◯ LOW [b,g]	There are significant reductions in exacerbation rates with benralizumab compared to placebo in those patients with baseline blood eosinophil counts <300/µL and ≥300/ µL. However there are no statistically significant differences between subgroups.
Adverse events follow up: range 48 weeks to 56 weeks № of participants: 1525 (2 RCTs) [1,3] Importance: IMPORTANT	The proportion of patients treated with benralizumab who had any adverse event compared to placebo were: Eosinophil < 300/uL: 76.3% versus 79.8%, RR (95%CI) = 0.95 (0.87 to 1.04), Absolute effect = 40 fewer per 1,000 (from 104 fewer to 32 more), n=515. Eosinophil ≥ 300/uL: 73.6% versus 75.9%, RR (95%CI) = 0.98 (0.87 to 1.10), Absolute effect = 15 fewer per 1,000 (from 99 fewer to 76 more), n=1010. Test for subgroup differences, p=0.75.[n]  	⊕⊕◯◯ LOW [k,l,m]	There is no significant increase in the incidence of adverse events with benralizumab compared to placebo in patients with baseline blood eosinophil counts <300/µL and ≥300/ µL. There are no statistically significant differences between subgroups.

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI) Difference	Certainty	What happens
Serious adverse events follow up: range 48 weeks to 56 weeks № of participants: 1525 (2 RCTs) [1,3] Importance: IMPORTANT	The proportion of patients treated with benralizumab who had any serious adverse event compared to placebo were: Eosinophil < 300/uL: 11.5% versus 15.3%, RR (95%CI) = 0.73 (0.32 to 1.66), Absolute effect = 41 fewer per 1,000 (from 104 fewer to 101 more), n=515. Eosinophil ≥ 300/uL: 11.7% versus 13.6%, RR (95%CI) = 0.86 (0.62 to 1.19), Absolute effect = 19 fewer per 1,000 (from 52 fewer to 26 more), n=1010. Test for subgroup differences, p=0.71.  	⊕◯◯◯ VERY LOW [l,o,p]	There is no significant increase in the incidence of serious adverse events with benralizumab compared to placebo in patients with baseline blood eosinophil counts <300/µL and ≥300/ µL. There are no statistically significant differences between subgroups.
Systemic steroids (absolute final dose) follow up: 28 weeks № of participants: 148 (1 RCT) [5] **Study participants meet criteria for the diagnosis of severe asthma defined by the ERS/ATS Guidelines on Severe Asthma[7]** Importance: CRITICAL	The median oral glucocorticoid dose (range) at the final visit (week 28) in the subgroup with baseline blood eosinophils ≥150 to <300/µL was: 5.0 mg/day (0.0–15.0) in patients who received placebo (n=11) and 6.25 mg/day (0.0–30.0) in patients who received benralizumab (n=12). In the subgroup with baseline blood eosinophils ≥300/µL: 10.0 mg/day (0.0–40.0) in patients who received placebo (n=64) and 5.0 mg/day (0.0–25.0) in patients who received benralizumab (n=61). No statistical test comparing results has been reported.	⊕◯◯◯ VERY LOW [q,r]	Oral glucocorticoid dose is 5 mg/day less with benralizumab compared to placebo in the subgroup with baseline blood eosinophils ≥300/µL whereas in the subgroup with baseline blood eosinophils ≥150 to <300/µL oral glucocorticoid dose is 1.25 mg/day less with placebo. No statistcal test available.

Outcome № of participants (studies)	Relative effect (95% CI)	**Anticipated absolute effects (95% CI)**			Certainty	What happens
				Difference		
Systemic steroids (percent reduction) follow up: 28 weeks № of participants: 148 (1 RCT) [5] **Study participants meet criteria for the diagnosis of severe asthma defined by the ERS/ATS Guidelines on Severe Asthma[7]** Importance: CRITICAL	The median reduction in final oral glucocorticoid dose compared with baseline (range, %) in the subgroup with baseline blood eosinophils ≥150 to <300/µL was: 50.0% (0.0–100) in patients who received placebo (n=11) and 57.5% (-50.0–100) in patients who received benralizumab (n=12). In the subgroup with baseline blood eosinophils ≥300/µL: 0.0% (–150 to 100) in patients who received placebo (n=64) and 75.0% (–50.0 to 100) in patients who received benralizumab (n=61). No statistical test comparing results has been reported.				⨁◯◯◯ VERY LOW [q,r]	There were similar oral glucocorticoid dose reduction with benralizumab or placebo in the subgroup with baseline blood eosinophils ≥150 to <300/µL (50% and 57.7%) whereas in the subgroup with baseline blood eosinophils ≥300/µL the oral glucocorticoid dose reduction was 0% in placebo and 75% in benralizumab. No statistcal test available.

CI: Confidence interval; **FEV1:** forced expiratory volume in 1 second; **MCID:** minimal clinically important difference; **MD:** Mean difference; **SMD:** Standardised mean difference; **RCT**: randomised controlled trial; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Potential risk of bias associated with selective outcome reporting bias (ad hoc subgroup analysis in participants with blood eosinophil counts <300/µl in Castro 2014).

b. Three studies (Bleecker 2016, Castro 2014 and FitzGerald 2016) included a mixed population of patients with moderate and severe asthma.

c. A single study reported results for the subgroup with blood eosinophils counts <300/µL. This analysis included only 55 patients (4 in benralizumab arm and 51 in placebo arm).

d. Potential risk of bias associated with selective outcome reporting bias in participants with eosinophil counts <300/µl (ad hoc subgroup analysis in Castro 2014; analysis not specified in protocols of Bleecker 2016 and FitzGerald 2016).

e. The study included a mixed population of patients with moderate and severe asthma.

f. For both subgroups the ends of the 95% confidence interval include appreciable clinical harm (MCID = 0.5) and no benefit and could lead to opposite clinical decisions. Results from single study with only 51 patients.

g. Potential risk of bias associated with selective outcome reporting bias in participants with baseline blood eosinophil counts <300 cells/μl: ad hoc subgroup analysis in Castro 2014; additional analysis in patients with blood eosinophil counts <150/μL, 150-299/μL, 300-449/μL and ≥450/μL were stated in the protocol but not reported by Bleecker 2016 and FitzGerald 2016.

h. For the subgroup with baseline blood eosinophils <300 cells/μl the ends of the 95% confidence interval include appreciable clinical benefit and no benefit and could lead to opposite clinical decision.

i. FEV1% was not specified as pre- or post-bronchodilator in Park 2016 but we have assumed it to be pre-bronchodilator.

j. For both subgroups the ends of the 95% confidence interval include appreciable clinical harm (MCID = 10.38%) and no benefit and could lead to opposite clinical decisions. Results from single study with only 51 patients.

k. I^2=65% (p=0.09) may represent substantial statistical heterogeneity in the subgroup with baseline eosinophil count ≥300 cells/μl.

l. The studies included a mixed population of patients with moderate and severe asthma.

m. This judgement was based on a arbitrary clinical decision threshold of 15% increase or decrease in absolute effect.

n. There was a high incidence of adverse events in both benralizumab and placebo groups. The apparent benefit from benralizumab might be explained by a reduction of asthma-related adverse events with the active drug.

o. I^2=69% (p=0.07) may represent substantial statistical heterogeneity in the subgroup with baseline eosinophil count <300 cells/μl.

p. This judgement was based on a arbitrary clinical decision threshold of 10% increase or decrease in absolute effect in the subgroup with baseline blood eosinophil count <300 cells/μl.

q. Potential risk of bias associated with selective outcome reporting bias: the protocol for Nair 2017 specified that percentage reduction in oral glucocorticoid dose would be summarized by treatment group in patients with baseline blood eosinophil counts 150-299/μL, ≥300/μL, 300-450/μL and >450/μL separately. However results have not been reported for patients with 300-450 eosinophils/μL and >450 eosinophils/μL.

r. 95% confidence intervals could not be obtained and data from single study including only 148 patients.

References

1. Fitzgerald JM, Bleecker ER, Nair P, et al. Benralizumab, an anti-interleukin-5 receptor alpha monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2016; 388: 2128–2141.

2. 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 Respiratory Medicine 2014; 2: 878–890.

3. Bleecker ER, FitzGerald JM, Chanez P, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β2-agonists (SIROCCO):a randomised, multicentre, placebo-controlled phase 3 trial. Lancet 2016; 388: 2115–2127..

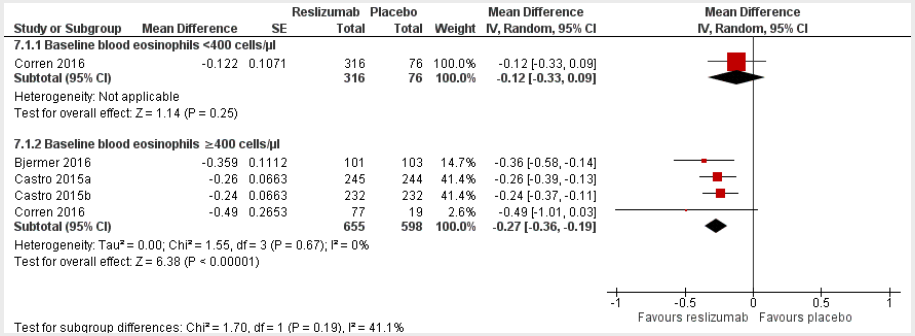
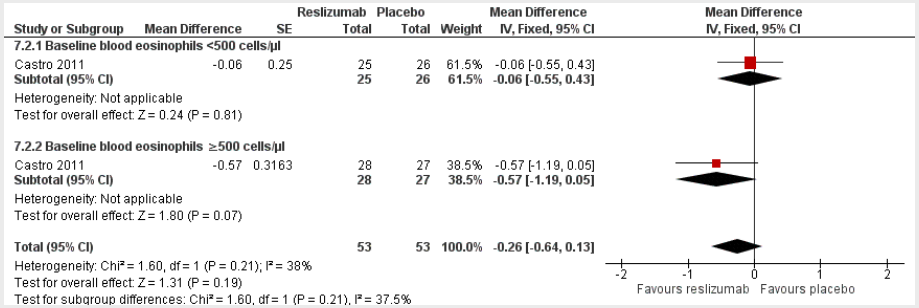
4. Park HS, Kim MK, Imai N, Nakanishi T, Adachi M, Ohta K, Tohda Y. A Phase 2a Study of Benralizumab for Patients with Eosinophilic Asthma in South Korea and Japan. Int Arch Allergy Immunol 2016; 169:135-145.

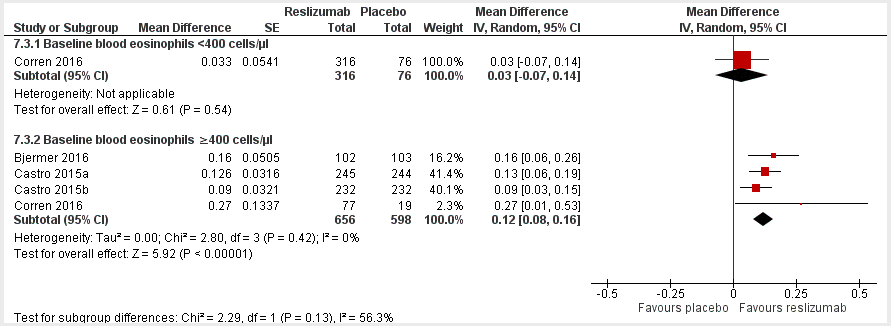
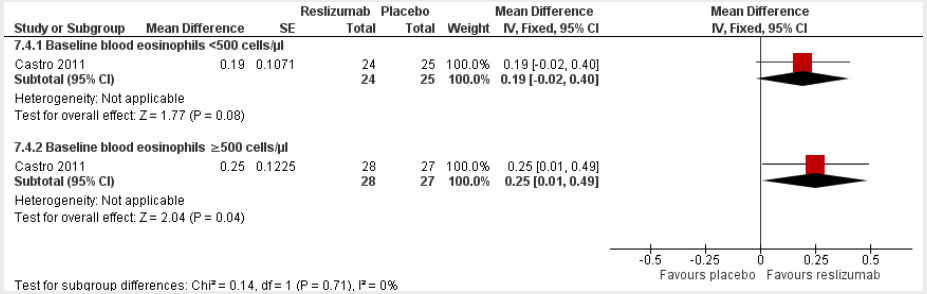
5. Nair P, Wenzel SE, Rabe KF, et al. Oral Glucocorticoid-Sparing Effect of Benralizumab in Severe Asthma. New England Journal of Medicine 2017; 376: 2448-2458.

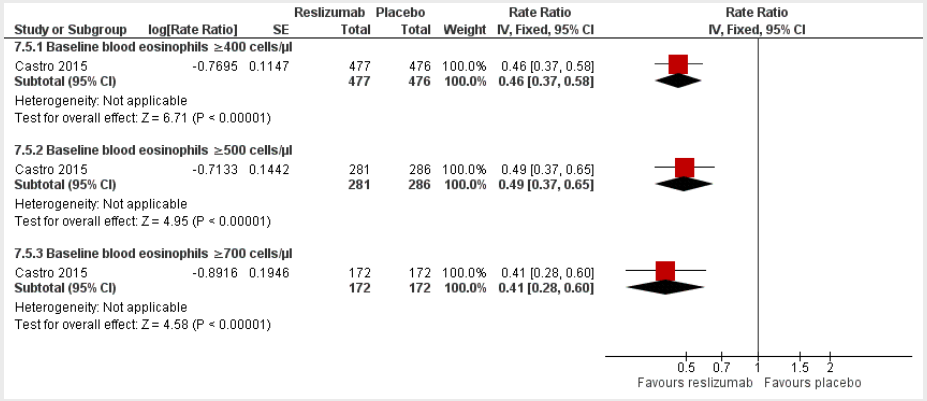
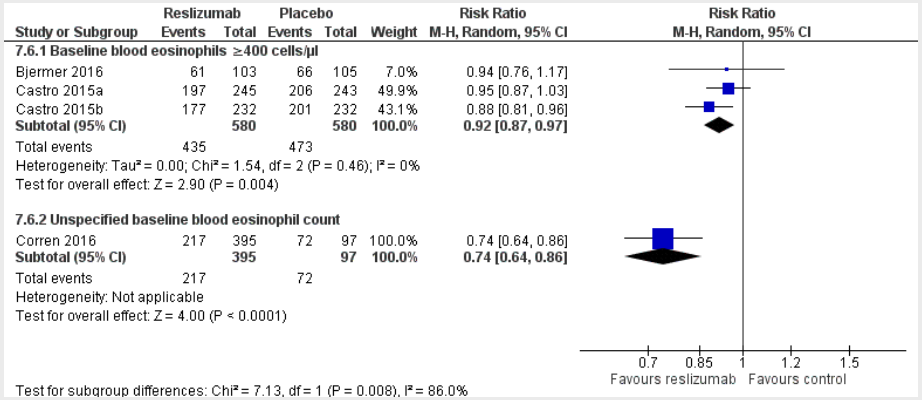
6. Santanello NC, Zhang J, Seidenberg B, Reiss TF, Barber BL. What are minimal important changes for asthma measures in a clinical trial? Eur Respir J 1999; 14: 23-27.

7, Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J 2014; 43: 343-373.

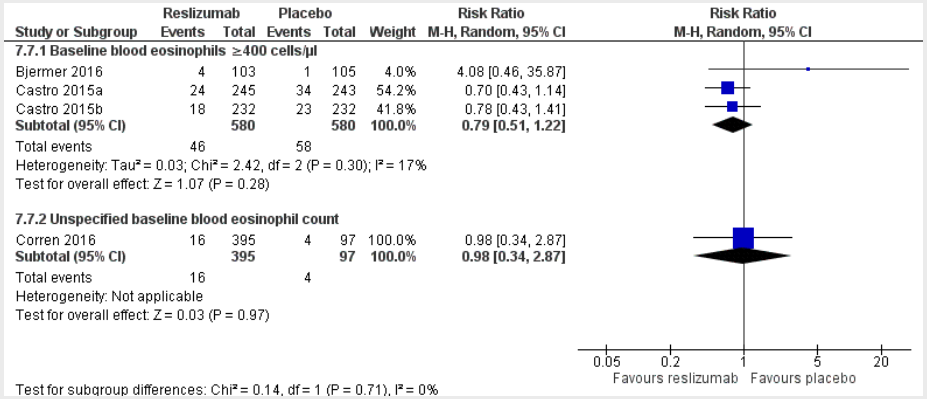
GRADE Evidence Profile: RESLIZUMAB (according to baseline number of blood eosinophils)

Outcome № of participants (studies)	Relative effect (95% CI)	**Anticipated absolute effects (95% CI)** **Difference**	Certainty	What happens
Asthma control (change from baseline) assessed with: Asthma Control Questionnaire (ACQ-7); Scale from: 0 to 6; lower values indicate better asthma control; MCID 0.5 follow up: range 16 weeks to 52 weeks № of participants: 1645 (4 RCTs) [1,2,3] Importance: CRITICAL	Mean change from baseline in ACQ-7 score in patients treated with reslizumab compared to placebo were: Eosinophil <400/µL: Mean difference (95% CI) = -0.12 (-0.33 to 0.09), n=392; Eosinophil ≥400/µL: Mean difference (95% CI) = -0.27 (-0.36 to -0.19), n=1253. Test for subgroup differences, p=0.19.  	⊕⊕⊕◯ MODERATE [a]	There are significant improvements in asthma control assessed by the ACQ-7 with reslizumab compared to placebo in patients with baseline blood eosinophil counts ≥400/µL but not <400/µL. However there are no statistically significant differences between subgroups.
Asthma control (change from baseline) assessed with: Asthma Control Questionnaire (ACQ-7); Scale from: 0 to 6; lower values indicate better asthma control; MCID 0.5 follow up: 15 weeks № of participants: 106 (1 RCT) [4] **<u>Study participants meet criteria for the diagnosis of severe asthma defined by the ERS/ATS Guidelines on Severe Asthma</u>**[5] Importance: CRITICAL	Mean change from baseline in ACQ-7 score in patients treated with reslizumab compared to placebo were: Eosinophil <500/µL: Mean difference (95% CI) = -0.06 (-0.55 to 0.43), n=51; Eosinophil ≥500/µL: Mean difference (95% CI) = -0.57 (-1.19 to 0.05), n=55. Test for subgroup differences, p=0.21.  	⊕◯◯◯ VERY LOW [b,c]	There are no significant improvements in asthma control assessed by the ACQ-7 with reslizumab compared to placebo in patients with baseline blood eosinophil counts <500/µL or ≥500/µL. There are no statistically significant differences between subgroups.

Outcome № of participants (studies)	Relative effect (95% CI)	**Anticipated absolute effects (95% CI)** **Difference**	Certainty	What happens
Lung function (Pre-bronchodilator FEV1 litres) follow up: range 16 weeks to 52 weeks MCID 0.23 litre[6] № of participants: 1646 (4 RCTs) [1,2,3] Importance: IMPORTANT	Mean change from baseline in pre-bronchodilator FEV1 (litres) in patients treated with reslizumab compared to placebo were: Eosinophil <400/µL: Mean difference (95% CI) = 0.03 L (-0.07 to 0.14 L), n=392; Eosinophil ≥400/µL: Mean difference (95% CI) = 0.12 L (0.08 to 0.16 L), n=1254. Test for subgroup differences, p=0.13.  	⊕⊕⊕◯ MODERATE [a]	There is a significant increase in pre-BD FEV1 (litres) with reslizumab compared to placebo in the subgroup of patients with blood eosinophil counts ≥400/µL, whereas there are no differences for those patients with blood eosinophils <400/µL. However there are no statistically significant differences between subgroups.
Lung function (Pre-bronchodilator FEV1 litres) follow up: 15 weeks MCID 0.23 litre[6] № of participants: 104 (1 RCT) [4] **Study participants meet criteria for the diagnosis of severe asthma defined by the ERS/ATS Guidelines on Severe Asthma[5]** Importance: IMPORTANT	Mean change from baseline in pre-bronchodilator FEV1 (litres) in patients treated with reslizumab compared to placebo were: Eosinophil <500/µL: Mean difference (95% CI) = 0.19 L (-0.02 to 0.40 L), n=49; Eosinophil ≥500/µL: Mean difference (95% CI) = 0.25 L (0.01 to 0.49 L), n=55. Test for subgroup differences, p=0.71.  	⊕◯◯◯ VERY LOW [b,d]	There is a significant increase in pre-BD FEV1 (litres) with reslizumab compared to placebo in the subgroup of patients with blood eosinophil counts ≥500/µL, whereas there are no differences for those patients with blood eosinophils <500/µL. However there are no statistically significant differences between subgroups.

Outcome № of participants (studies)	Relative effect (95% CI)	**Anticipated absolute effects (95% CI)**		Certainty	What happens
			Difference		
Rate of any exacerbation follow up: 52 weeks № of participants: 953 (2 RCTs) [2] Importance: CRITICAL	Annualised mean exacerbation rates per patient treated with reslizumab compared to placebo were: Eosinophil ≥400/µL: 0.84 versus 1.81 events/patient/year, Rate ratio (95%CI) = 0.46 (0.37, 0.58), n=953. Eosinophil ≥500/µL: Rate ratio (95%CI) = 0.49 (0.37 to 0.65), n=567; Eosinophil ≥700/µL: Rate ratio (95%CI) = 0.41 (0.28 to 0.60), n=344. Exacerbation rates were not specified for the subgroups ≥500 and ≥700 eosinophils/µL  	⊕⊕◯◯ LOW [a,b]	There are significant reductions in exacerbation rates with reslizumab compared to placebo in those patients with baseline blood eosinophil counts ≥400/µL, ≥500/µL and ≥700//µL. However there is appreciable overlap of the 95% CIs.
Adverse events follow up: range 16 weeks to 52 weeks № of participants: 1652 (4 RCTs) [1,2,3] Importance: IMPORTANT	The proportion of patients treated with reslizumab who had any adverse event compared to placebo were: Eosinophil ≥ 400/µL: 75% versus 81.6%, RR (95%CI) = 0.92 (0.87 to 0.97), Absolute effect = 65 fewer per 1,000 (from 106 fewer to 24 fewer), n=1160. Unspecified baseline blood eosinophil counts: 54.9% versus 74.2%, RR (95%CI) = 0.74 (0.64 to 0.86), Absolute effect = 193 fewer per 1,000 (from 267 fewer to 104 fewer), n=492. Test for subgroup differences, p=0.008. [e,f]  	⊕⊕◯◯ LOW [a,g]	There are significant decreases in the incidence of adverse events with reslizumab compared to placebo in patients with baseline blood eosinophil counts ≥400/µL and with unspecified baseline blood eosinophil counts. There are statistically significant differences between subgroups.

Outcome № of participants (studies)	Relative effect (95% CI)	**Anticipated absolute effects (95% CI)**			Certainty	What happens
				Difference		
Serious adverse events follow up: range 16 weeks to 52 weeks № of participants: 1652 (4 RCTs) [1,2,3] Importance: IMPORTANT	The proportion of patients treated with reslizumab who had any serious adverse event compared to placebo were: Eosinophil ≥ 400/µL: 7.9% versus 10.0%, RR (95%CI) = 0.79 (0.51 to 1.22), Absolute effect = 21 fewer per 1,000 (from 49 fewer to 22 more), n=1160. Unspecified baseline blood eosinophil counts: 4.1% versus 4.1%, RR (95%CI) = 0.98 (0.34 to 2.87), Absolute effect = 1 fewer per 1,000 (from 27 fewer to 77 more), n=492. Test for subgroup differences, p=0.71. [e]				⊕⊕⊕◯ MODERATE [a,h]	There are no significant increases in the incidence of serious adverse events with reslizumab compared to placebo in patients with baseline blood eosinophil counts ≥400/µL and with unspecified baseline blood eosinophil counts. There are no statistically significant differences between subgroups.



CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. All studies included a mixed population of patients with moderate and severe asthma.

b. Potential risk of bias associated with selective outcome reporting bias (post hoc subgroup analysis).

c. For both subgroups the ends of the 95% confidence interval include appreciable clinical benefit (MCID 0.5) and no benefit and could lead to opposite clinical decisions. Results from single study with only 106 patients.

d. For both subgroups the ends of the 95% confidence interval include appreciable clinical benefit (MCID 0.23 L) and no benefit and could lead to opposite clinical decisions. Results from single study with only 104 patients.

e. The trial by Corren 2016, which provided results for the subgroup "Unspecified baseline blood eosinophil counts" reported that eosinophils ≥ 400 cells/µL were observed in 20% of patients at baseline , distributed similarly between treatment groups.

f. There was a high incidence of adverse events in both reslizumab and placebo groups. The apparent benefit from reslizumab might be explained by a reduction of asthma-related adverse events with the active drug.

g.This judgement was based on a arbitrary clinical decision threshold of 15% increase or decrease in absolute effect in the subgroup with unspecified baseline blood eosinophil counts.

h. This judgement was based on a arbitrary clinical decision threshold of 10% increase or decrease in absolute effect.

References

1. Corren J, Weinstein S, Janka L, Zangrilli J, Garin M. Phase 3 Study of Reslizumab in Patients With Poorly Controlled Asthma: Effects Across a Broad Range of Eosinophil Counts. Chest 2016; 150: 799-810.

2. 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: 355-366.

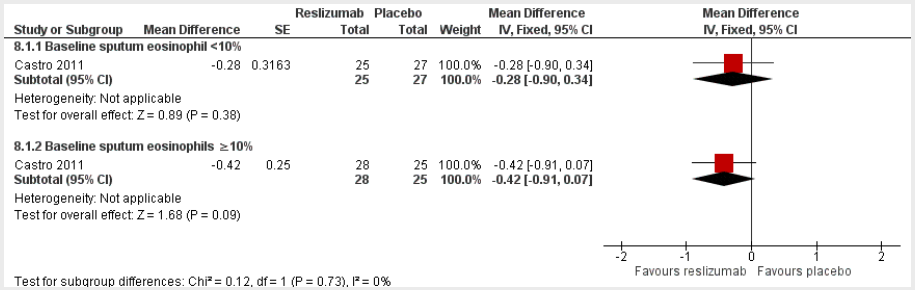
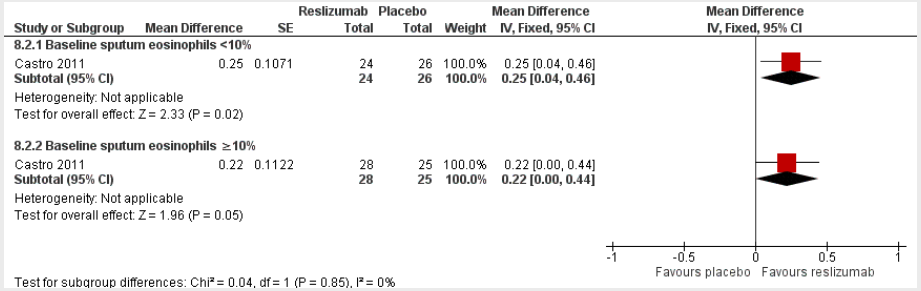
3. Bjermer L, Lemiere C, Maspero J, Weiss S, Zangrilli J, Germinaro M. Reslizumab for Inadequately Controlled Asthma With Elevated Blood Eosinophil Levels: A Randomized Phase 3 Study. Chest 2016; 150: 789-798.

4. 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: 1125-1132.

5. Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J 2014; 43: 343-373.

6.Santanello NC, Zhang J, Seidenberg B, Reiss TF, Barber BL. What are minimal important changes for asthma measures in a clinical trial? Eur Respir J 1999; 14: 23-27.

GRADE Evidence Profile: RESLIZUMAB (according to baseline sputum eosinophils - %)

Outcome № of participants (studies)	Relative effect (95% CI)	**Anticipated absolute effects (95% CI)** **Difference**	Certainty	What happens
Asthma control (change from baseline) assessed with: Asthma Control Questionnaire (ACQ-7); Scale from: 0 to 6; lower values indicate better asthma control; MCID 0.5 follow up: 15 weeks № of participants: 105 (1 RCT) [1] **Study participants meet criteria for the diagnosis of severe asthma defined by the ERS/ATS Guidelines on Severe Asthma[3]** Importance: CRITICAL	Mean change from baseline in ACQ-7 score in patients treated with reslizumab compared to placebo were: sputum eosinophils <10%: Mean difference (95% CI) = -0.28 (-0.90 to 0.34), n=52; sputum eosinophils ≥10%: Mean difference (95% CI) = -0.42 (-0.91 to 0.07), n=53. Test for subgroup differences, p=0.73.  	⊕◯◯◯ VERY LOW [a,b]	There are no significant improvements in asthma control assessed by the ACQ-7 with reslizumab compared to placebo in patients with baseline sputum eosinophils <10% or ≥10%. There are no statistically significant differences between subgroups.
Lung function (Pre-bronchodilator FEV1 litres) follow up: 15 weeks MCID 0.23 litre[2] № of participants: 103 (1 RCT) [1] **Study participants meet criteria for the diagnosis of severe asthma defined by the ERS/ATS Guidelines on Severe Asthma[3]** Importance: IMPORTANT	Mean change from baseline in pre-bronchodilator FEV1 (litres) in patients treated with reslizumab compared to placebo were: sputum eosinophils <10%: Mean difference (95% CI) = 0.25 L (0.04 to 0.46 L), n=50; sputum eosinophils ≥10%: Mean difference (95% CI) = 0.22 L (0 to 0.44 L), n=53. Test for subgroup differences, p=0.85.  	⊕◯◯◯ VERY LOW [a,c]	There is a significant increase in pre-BD FEV1 (litres) with reslizumab compared to placebo in the subgroup of patients with sputum eosinophils <10% but not in pacient with ≥10% sputum eosinophils. There are no statistically significant differences between subgroups.

BD: bronchodilator; **CI:** Confidence interval; **FEV1:** forced expiratory volume in 1 second; **MCID:** minimal clinically important difference; **MD:** Mean difference; **RCT**: randomised controlled trial

Outcome № of participants (studies)	Relative effect (95% CI)	**Anticipated absolute effects (95% CI)**			Certainty	What happens
				Difference		

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

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Explanations

a. Potential risk of bias associated with selective outcome reporting bias (post hoc subgroup analysis).

b. For both subgroups the ends of the 95% confidence interval include appreciable clinical benefit (MCID 0.5) and no benefit and could lead to opposite clinical decisions. Results from single study with only 105 patients.

c. For both subgroups the ends of the 95% confidence interval include appreciable clinical benefit (MCID 0.23 L) and no benefit and could lead to opposite clinical decisions. Results from single study with only 103 patients.

References

1. 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: 1125-1132.

2. Santanello NC, Zhang J, Seidenberg B, Reiss TF, Barber BL. What are minimal important changes for asthma measures in a clinical trial? Eur Respir J 1999; 14: 23-27.

3. Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J 2014; 43: 343-373.

Evidence to Decision Framework

Should the level of eosinophils (in blood or sputum) be used to guide the initiation of a monoclonal antiI-IL5 strategy in adults and children with severe asthma?

POPULATION:	Adults and children with severe asthma	**BACKGROUND:**	Patients with severe asthma are characterized by uncontrolled symptoms and signs despite treatment with high dose steroids and bronchodilators, or require these therapies to maintain control. IL-5 is the main cytokine involved in the activation of eosinophils which are a classic feature of atopic severe asthma. Monoclonal antibodies have been developed that bind the IL-5 cytokine or receptor. The three drugs in this category: mepolizumab, reslizumab and benralizumab have been shown to be efficacious in randomized controlled trials at improving outcomes. However, patients exposed to this therapy have variable therapeutic response to this class of drugs which may reflect differences in their underlying biology. This systematic review and meta-analysis investigates whether specific levels of eosinophilia in blood or sputum can be used as a biomarker to predict therapeutic response to monoclonal anti-IL5 therapies.
INTERVENTION:	Use of Eosinophil level in blood or sputum identify patients for therapy with an anti-interleukin 5 strategy (monoclonal antibodies directed against the interleukin 5 or its receptor)		
COMPARISON:	Treatment of all with anti-interleukin 5 strategy (monoclonal antibodies directed against the interleukin 5 or its receptor)		
MAIN OUTCOMES:	Respiratory symptoms Lung function Exacerbation rate Adverse events Serious adverse events		

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○Don't know	Results from research evidence (studies) There were 13 RCT studies (PMID: 27056586; 27609408; 25306557; 25736990; 28395936; 27018175; 27609406; 28530840; 27177493; 27097165; 21852542) that performed either pre-specified or post hoc subgroup analyses evaluating different treatment responses based on baseline sputum or blood eosinophil levels. The results across anti-IL 5 medications and well as biomarker level and type varies substantially for outcomes. An important outcome for patients includes rate of exacerbation. Blood eosinophils were the most typically measured biomarker and was available for all the medications. In one study (PMID: 27177493), baseline serum eosinophils of ≥500/uL were associated with a significantly greater response to therapy for mepolizumab only. For this outcome, there was a 73% reduction in exacerbations amongst those with a blood eosinophil level of ≥500/uL compared to 36-39% non-statistically significant reduction in subgroups with eosinophil levels of 150 to <300 cells/ cells/µL and 300 to <500 cells/µL, respectively. Notably mepolizumab reduced exacerbation rates in all the subgroups defined by different baseline eosinophil thresholds (≥150, ≥300, ≥400 and ≥500 cells/µL) . Blood eosinophil levels of greater than 300/µL were associated with improvement in quality of life after treatment with benralizumab but there was no significant difference between subgroups (PMID: 27609408; 25306557; 27609406). Sputum eosinophil level was only considered in one study of reslizumab. Sputum levels were categorized as > or ≥ 10%. There were no differences found between groups. Higher blood sputum levels were associated with a greater improvement in asthma control; however the differences between levels were not significant. As per PICO1, all subjects at eosinophil levels ≥150/uL experienced a significant reduction in exacerbations. Notably, studies of iv mepolizumab were excluded since only subcutaneous mepolizumab have been approved by the FDA/EMA.	Panel considerations One single-blind, placebo controlled sequential trial (PMID: 28915080) assessed treatment response of weight-adjusted IV reslizumab in patients previously treated with 100-mg SC mepolizumab. They reported that persistently high levels of eosinophils (blood eos >300/uL and sputum eos >3%) after treatment with mepolizumab characterized non-responders. Treatment of this group with reslizumab lead to improvements in their symptoms and eosinophil levels.

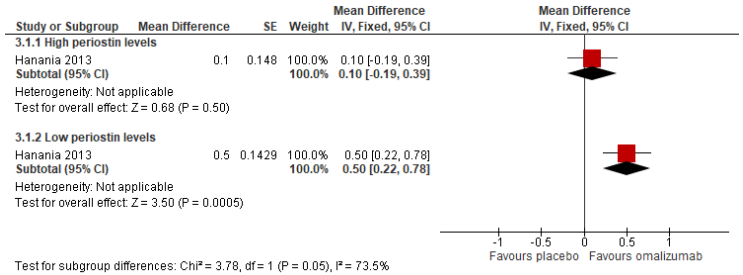
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	There were 5 papers reporting results of six RCTs (PMID: 27609406, 27609408, 27056586, 25736990, 27018175) that assessed adverse events. There was no data in mepolizumab. The data suggested that overall there was no difference in adverse events amongst those with higher vs lower eosinophil counts for benralizumab. For Reslizumab, the fewest adverse events occurred in the group who had no data on eosinophil count. There was a slight reduction in the number of adverse events amongst those with an eosinophil count of ≥400/uL but it was 8% lower (95% CI: 3, 13%).	There was a high incidence of adverse events in both the active-drug (benralizumab and reslizumab) and placebo groups. The apparent benefit from the active-drugs might be explained by a reduction of asthma-related adverse events with the active drugs.
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ● Very low ○ Low ○ Moderate ○ High ○ No included studies	The level of evidence is very low. The evidence is based on pre-specified or post-hoc subgroup analyses of RCTs that tested whether baseline eosinophil levels were predictive of the therapeutic response to an anti-IL5 strategy. Therefore, there is a potential bias of selective outcome reporting bias. For studies of benralizumab, moderate and severe asthmatics were selected.	
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes		There is no uncertainty in how patients and clinicians value asthma exacerbations. However, there is some uncertainty the impact of measurement of eosinophil level at baseline in predicting outcomes. The data suggests that patients with severe asthma benefit from an anti-IL5 strategy and those with higher levels >300-500/uL derive greater benefit than those with a level of <150/uL. Different patients may value the benefits / harms of the intervention differently (for instance more value to avoid harms compared to anticipated benefits).

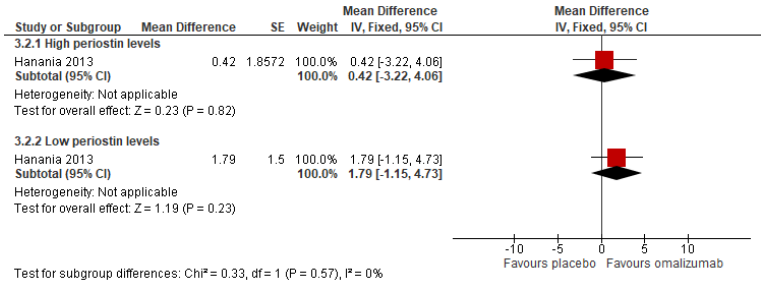
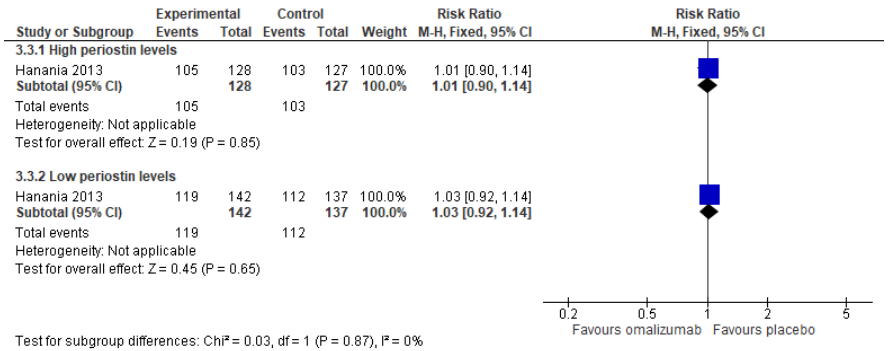
BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies ○ Don't know	Most of the data presented suggests that patients with severe asthma benefit from an anti-IL5 strategy. Furthermore, there is some evidence that further benefit may be derived in patients with higher levels of baseline blood eosinophilia > 300 – 500/uL compared to those with an eosinophil level <150/uL. Only mepolizumab showed a significant reduction in asthma exacerbation amongst patients with an eosinophil level of ≥500/uL compared to other levels > 150/uL. However, even subjects with a eosinophil levels between 150 and 300/uL benefited from therapy compared to placebo.	
COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No research evidence available.	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ○ Low ○ Moderate ○ High ● No included studies	No research evidence available on the cost of the intervention (studying eosinophil level).	Cost and feasibility differ based on the biomarker. Blood eosinophil levels are easily ascertained in most blood laboratories; sputum eosinophils are primarily available only in specialized centers.
EQUITY	**What would be the impact on health equity?** ○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased	No research evidence available.	Consider: Blood eosinophils are very variable and can fluctuate dramatically with oral steroid treatment. In areas, where oral steroid therapy is more common than the use of combination inhalers, blood eosinophils

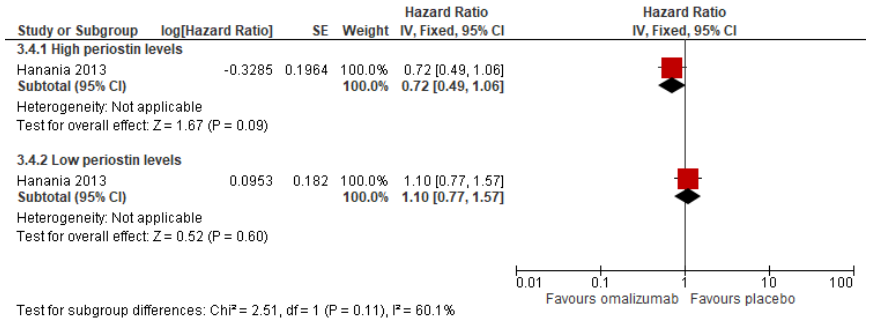
	○ Varies ● Don't know		may be lower. Are there groups or settings that might be disadvantaged in relation to the problem or options that are considered? Are there plausible reasons for anticipating differences in the relative effectiveness of the option for disadvantaged groups or settings? Are there different baseline conditions across groups or settings that affect the absolute effectiveness of the option or the importance of the problem for disadvantaged groups or settings? Are there important considerations that should be made when implementing the intervention (option) in order to ensure that inequities are reduced, if possible, and that they are not increased?
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ● Don't know	No research evidence available.	There are no data on the acceptability of baseline eosinophil measurement. More data is required to determine whether the use of biomarkers such as eosinophil level to determine therapeutic response would be useful and acceptable. However, as noted above, blood measurement of eosinophils is more easily accessible in standard clinical laboratories than sputum eosinophil measurement.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	No research evidence available.	Patients may find that some practicalities limit the use / make less feasible the use of the recommended intervention for example the use of sputum eosinophils as it requires a specialized center. It is feasible to implement baseline blood measurement in most settings.

Should a measurement of a specific biomarker be used, in addition to total IgE level, to guide initiation of treatment with a monoclonal anti-IgE antibody in adults and children with severe asthma? (biomarkers being exhaled NO, peripheral or sputum eosinophils, and serum periostin)

GRADE Evidence Profile: OMALIZUMAB - PERIOSTIN

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	omalizumab	placebo	Relative (95% CI)	Absolute (95% CI)		
Reduction in exacerbation rates per patient Follow up: 48 weeks (higher percentage, better reduction)												
1 (534 participants)[1]	randomised trials	serious [a]	not serious	not serious	serious [b]	none	Relative reduction in exacerbation rate of omalizumab compared to placebo were: Periostin (≥50 ng/ml): 30% (95% CI: -2 to 51); p-value= 0.07 Periostin (<50 ng/ml): 3% (95% CI: -43 to 32); p-value= 0.94 Number of patients: 534; test for subgroup differences: no available				⨁⨁◯◯ LOW	
Change from baseline at week 48 in AQLQ Follow up: 48 weeks 7-point scale (7 = not impaired at all - 1 = severely impaired; higher values, better QoL)												
1 (534 participants)[1]	randomised trials	serious [a]	not serious	not serious	serious [b]	none	Mean change from baseline to week 48 of omalizumab compared to placebo were: Periostin (≥50 ng/ml): Least square mean difference= 0.10 (95% CI: -0.19 to 0.40); p-value= 0.51 Periostin(<50 ng/ml): Least square mean difference= 0.50 (95% CI: 0.22 to 0.77); p-value= 0.0005 Number of patients: 534; test for subgroup differences: P=0.05 [c] 				⨁⨁◯◯ LOW	
Change from baseline in % predicted FEV1 Follow up: 48 weeks (higher change, better outcome)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	omalizumab	placebo	Relative (95% CI)	Absolute (95% CI)		
1 (534 participants)[1]	randomised trials	serious [a]	not serious	not serious	serious [b]	none	Mean change from baseline to week 48 of omalizumab compared to placebo were: Periostin (≥50 ng/ml): Least square mean difference= 0.42 (95% CI: -3.22 to 4.06); p-value= 0.82 Periostin (<50 ng/ml): Least square mean difference= 1.79 (95% CI: -1.15 to 4.73); p-value= 0.23 Number of patients: 534; test for subgroup differences: P=0.57 [c] 			⊕⊕◯◯ LOW	
Adverse events Follow up: 48 weeks (higher values, worst outcome)												
1 (534 participants)[1]	randomised trials	serious [a]	not serious	not serious	serious [b]	none	Percentage of patients with treatment-related adverse events of omalizumab compared to placebo were: Periostin (≥50 ng/ml): 82% versus 81%; RR= 1.01 (95% CI= 0.90 to 1.14) Periostin (<50 ng/ml): 84% versus 82%; RR= 1.03 (95% CI= 0.92 to 1.14) Number of patients: 534; test for subgroup differences: P=0.87 			⊕⊕◯◯ LOW	
Time to first protocol asthma exacerbation Follow up: 48 weeks (lower values, better outcome)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	omalizumab	placebo	Relative (95% CI)	Absolute (95% CI)		
1 (534 participants)[1]	randomised trials	serious [a]	not serious	not serious	serious [b]	none	Time to first asthma exacerbation of omalizumab compared to placebo were: Periostin (≥50 ng/ml): HR= 0.72 (95% CI= 0.49 to 1.1) Periostin(<50 ng/ml): HR= 1.1 (95% CI= 0.77 to 1.6) Number of patients: 534; test for subgroup differences: P=0.11 			⊕⊕◯◯ LOW	

CI: Confidence interval

Explanations

a. Risk of bias due to a considerable number of patients was not evaluated at baseline for biomarker levels

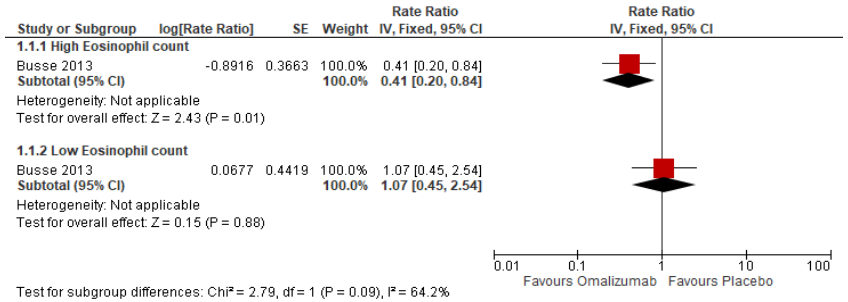
b. Optimal information size not reached for the main objective (and then for the subgroup analysis), reported by authors

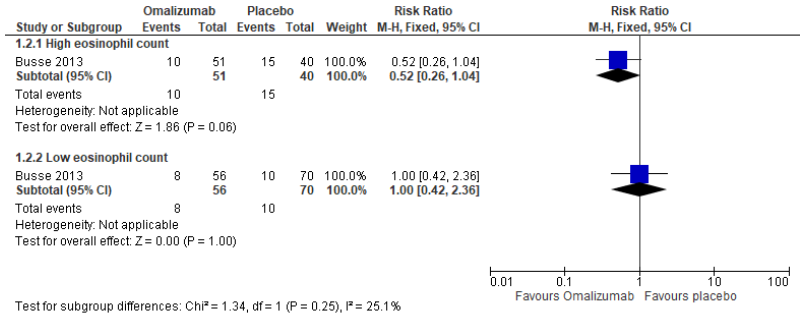
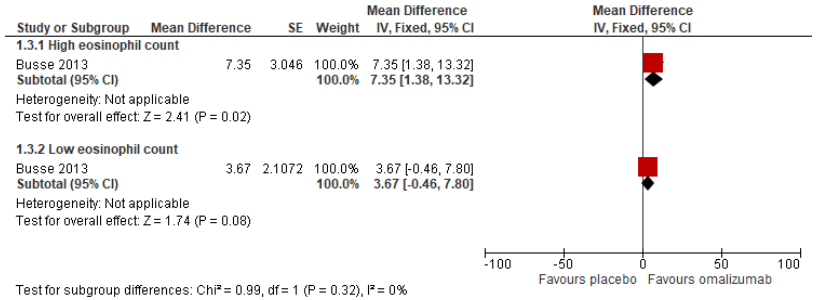
c. P values about Test for subgroup differences were estimated in RevMan and assuming that LSM is similar to Mean differences (just for descriptive purposes)

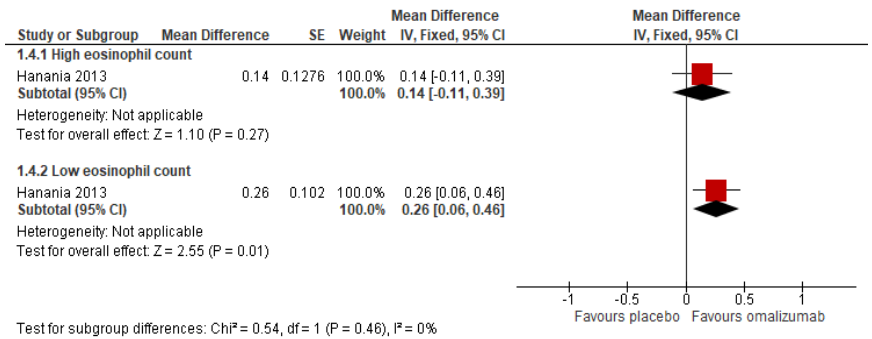
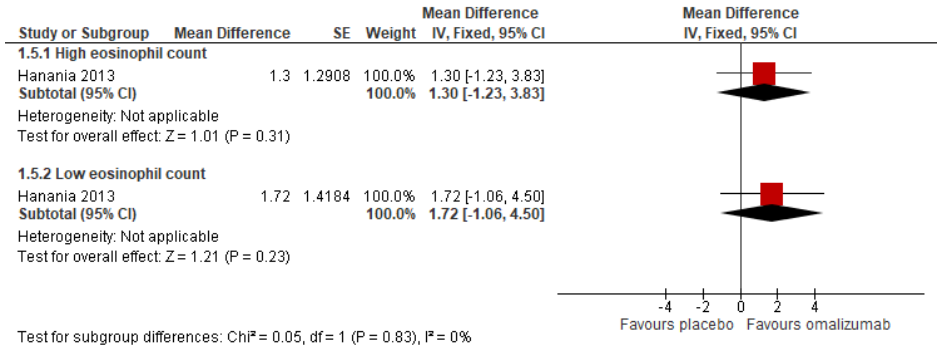
References

1. Hanania NA1, Wenzel S,Rosén K,Hsieh HJ,Mosesova S,Choy DF,Lal P,Arron JR,Harris JM,Busse W. Exploring the effects of omalizumab in allergic asthma: an analysis of biomarkers in the EXTRA study. Am J Respir Crit Care Med; 2013.

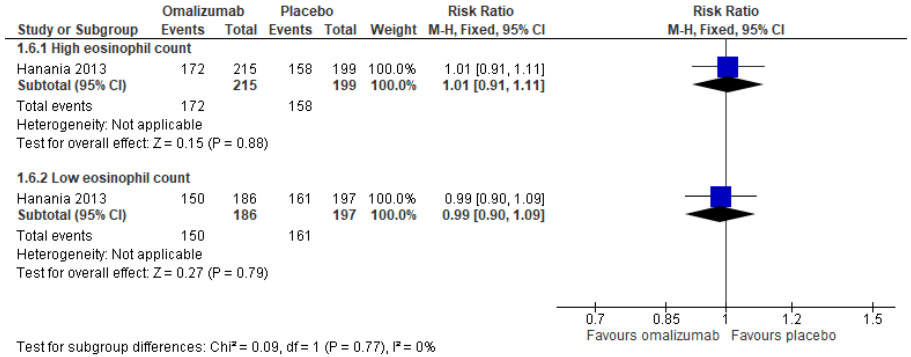
GRADE Evidence Profile: OMALIZUMAB - EOSINOPHIL

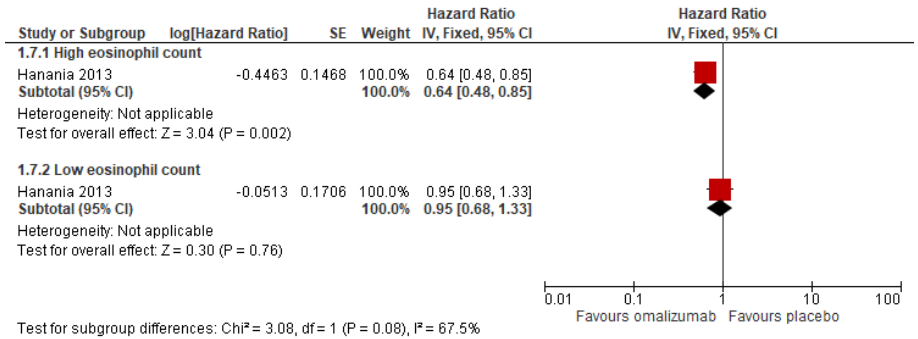
Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Omalizumab	placebo	Relative (95% CI)	Absolute (95% CI)		
Exacerbation rates per patient Follow up: 24 weeks (lower rates, better reduction)												
1 (217 participants) [1]	randomised trials	serious [a]	not serious	not serious	serious [b]	none	Exacerbation rate of omalizumab compared to placebo were: Eosinophil (≥300/uL): 0.25 vs 0.59, Rate ratio 0.41 (95%CI 0.20 to 0.82) Eosinophil (<300/uL): 0.17 vs 0.16, Rate ratio 1.07 (95%CI 0.45 to 2.53) Number of patients: 217; test for subgroup differences, p=0.09 	⊕⊕◯◯ LOW	
Reduction in exacerbation rates per patient Follow up: 48 weeks (higher percentage, better reduction)												
1 (797 participants) [2]	randomised trials	serious [a,c]	not serious	not serious	serious [b]	none	Relative reduction in exacerbation rate of omalizumab compared to placebo were: Eosinophil (≥260/uL): 32% (95% CI: 11 to 48); p-value= 0.005 Eosinophil (<260/uL): 9% (95% CI: -24 to 34); p-value= 0.54 Number of patients: 797; test for subgroup differences: no available			⊕⊕◯◯ LOW	
At least one exacerbation Follow up: 24 weeks (lower rates, better outcome)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Omalizumab	placebo	Relative (95% CI)	Absolute (95% CI)		
1 (217 participants) [1]	randomised trials	serious [a]	not serious	not serious	serious [b]	none	Exacerbation rate of omalizumab compared to placebo were: Eosinophil (≥300/uL): Risk ratio 0.52 (95%CI 0.26 to 1.04) Eosinophil (<300/uL): Risk ratio 1.00 (95%CI 0.42 to 2.36) Number of patients: 217; test for subgroup differences, p=0.25 		⊕⊕◯◯ LOW	
Relative change from baseline to week 24 in % predicted FEV1 (higher change, better outcome) Follow up: 24 weeks												
1 (217 participants) [1]	randomised trials	serious [a]	not serious	not serious	serious [b]	none	Relative change in % predicted FEV1 when omalizumab is compared to placebo were: Eosinophil (≥300/uL): Least squares mean treatment (ANOVA): 7.35% (95% CI: 1.38 to 13.31) Eosinophil (<300/uL): Least squares mean treatment (ANOVA): 3.67% (95% CI: -0.46 to 7.81) Number of patients: 217; test for subgroup differences: P= 0.32 [d] 		⊕⊕◯◯ LOW	
Change from baseline in Asthma Quality of Life Questionnaire (AQLQ) Follow up: 48 weeks 7-point scale (7 = not impaired at all - 1 = severely impaired; higher values, better QoL)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Omalizumab	placebo	Relative (95% CI)	Absolute (95% CI)		
1 (797 participants) [2]	randomised trials	serious [a,c]	not serious	not serious	serious [b]	none	Mean change from baseline to week 48 of omalizumab compared to placebo were: Eosinophil (≥260/uL): Least square mean difference= 0.14 (95% CI: -0.11 to 0.36); p-value= 0.29 Eosinophil (<260/uL): Least square mean difference= 0.26 (95% CI: 0.06 to 0.51); p-value= 0.01 Number of patients: 797; test for subgroup differences: P= 0.46 [d] 		⊕⊕◯◯ LOW	
Change from baseline in % predicted FEV1 Follow up: 48 weeks (higher change, better outcome)												
1 (797 participants) [2]	randomised trials	serious [a,c]	not serious	not serious	serious	none	Mean change from baseline to week 48 of omalizumab compared to placebo were: Eosinophil (≥260/uL): Least square mean difference= 1.3 (95% CI: -1.23 to 3.84); p-value= 0.31 Eosinophil (<260/uL): Least square mean difference= 1.72 (95% CI: -1.06 to 4.51); p-value= 0.02 Number of patients: 797; test for subgroup differences: P=0.83 [d] 		⊕⊕◯◯ LOW	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Omalizumab	placebo	Relative (95% CI)	Absolute (95% CI)		
Adverse events follow up: 48 weeks (higher values, worst outcome)												
1 (797 participants) [2,e]	randomised trials	serious [a,c]	not serious	not serious	serious [b]	none	Percentage of patients with treatment-related adverse events of omalizumab compared to placebo were: Eosinophil (≥260/uL): 80% versus 79.4%; RR= 1.01 (95% CI= 0.91 to 1.11) Eosinophil (<260/uL): 80.6% versus 81.7%; RR= 0.99 (95% CI= 0.90 to 1.09) Number of patients: 797 ; test for subgroup differences: P =0.77				⨁⨁◯◯ LOW	
Time to first asthma exacerbation Follow up: 48 weeks (lower values, better outcome)												
1 (797 participants) [2]	randomised trials	serious [a,c]	not serious	not serious	serious [b]	none	Time to first asthma exacerbation of omalizumab compared to placebo were: Eosinophil (≥260/uL): HR= 0.64 (95% CI= 0.48 to 0.86) Eosinophil (<260/uL): HR= 0.95 (95% CI= 0.68 to 1.3) Number of patients: 797; test for subgroup differences: P=0.08				⨁⨁◯◯ LOW	





CI: Confidence interval

Explanations

a. Risk of bias related to incomplete outcome data: eosinophil counts were not necessarily collected for all patients at baseline and may therefore have been missing at random depending on their availability in the original laboratory test records

b. Optimal information size not reached for the main objective (and then for the subgroup analysis), reported by authors

c. Potential risk of bias associated with selective reporting bias (subgroups analyses no stated in the protocol)

d. P values about Test for subgroup differences were estimated in RevMan and assuming that LSM is similar to Mean differences (just for descriptive purposes)

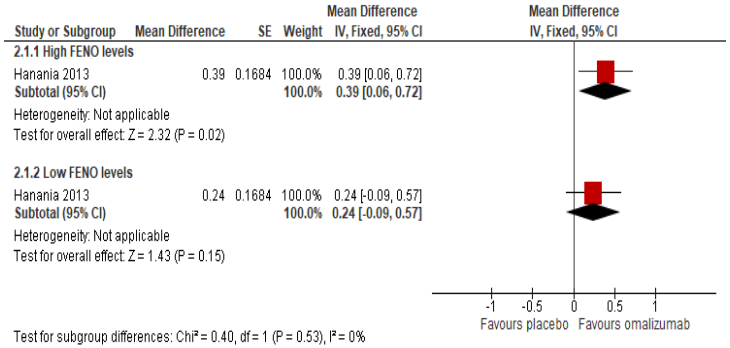
e. Only Hanania 2013 provided subgroup information for this outcome

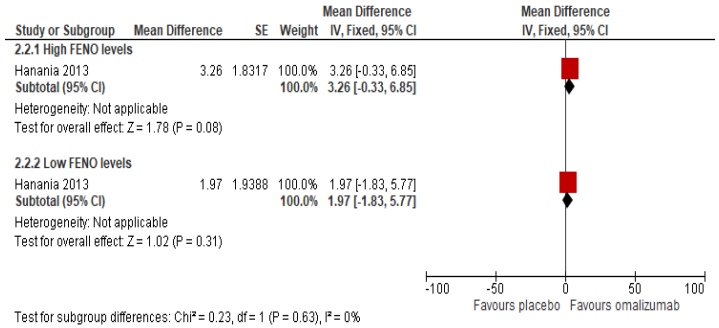
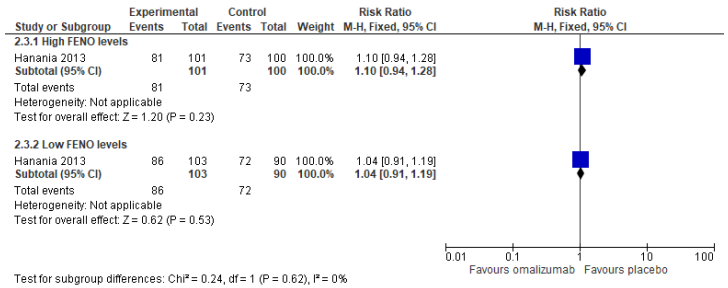
References

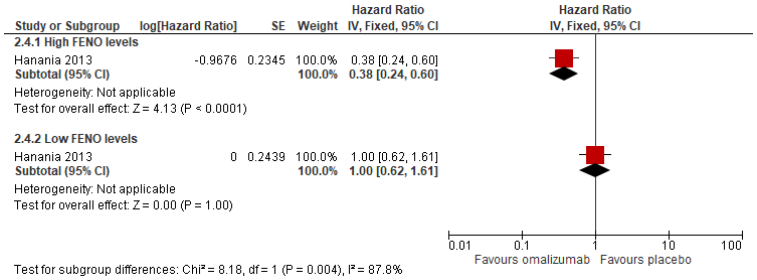
1. Busse W, Spector S,Rosén K,Wang Y,Alpan O. High eosinophil count: a potential biomarker for assessing successful omalizumab treatment effects. J Allergy Clin Immunol; 2013.

2. Hanania NA1, Wenzel S,Rosén K,Hsieh HJ,Mosesova S,Choy DF,Lal P,Arron JR,Harris JM,Busse W. Exploring the effects of omalizumab in allergic asthma: an analysis of biomarkers in the EXTRA study. Am J Respir Crit Care Med; 2013.

GRADE Evidence Profile: OMALIZUMAB – FeNO

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	omalizumab	placebo	Relative (95% CI)	Absolute (95% CI)		
Reduction in exacerbation rates per patient Follow up: 48 weeks (higher percentage, better reduction)												
1 (394 participants)[1]	randomised trials	serious [a]	not serious	not serious	serious [b]	none	Relative reduction in exacerbation rate of omalizumab compared to placebo were: FENO(≥19.5 ppb): 53% (95% CI: 37 to 70); p-value= 0.001 FENO(<19.5 ppb): 16% (95% CI: -32 to 46); p-value= 0.45 Number of patients: 394; test for subgroup differences: no available				⨁⨁◯◯ LOW	
Change from baseline to 48 week in AQLQ Follow up: 48 weeks 7-point scale (7 = not impaired at all - 1 = severely impaired; Higher values, better QoL)												
1 (394 participants)[1]	randomised trials	serious [a]	not serious	not serious	serious [b]	none	Mean change from baseline to week 48 of omalizumab compared to placebo were: FENO (≥19.5 ppb): Least square mean difference= 0.39 (95% CI: 0.06 to 0.73); p-value= 0.02 FENO (<19.5 ppb): Least square mean difference= 0.24 (95% CI: -0.09 to 0.57); p-value= 0.16 Number of patients: 394; test for subgroup differences: P= 0.53 [c] 				⨁⨁◯◯ LOW	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	omalizumab	placebo	Relative (95% CI)	Absolute (95% CI)		
Change from baseline in % predicted FEV1 Follow up: 48 weeks (higher change, better outcome)												
1 (394 participants)[1]	randomised trials	serious [a]	not serious	not serious	serious [b]	none	Mean change from baseline to week 48 of omalizumab compared to placebo were: FENO (≥19.5 ppb): Least square mean difference= 3.26 (95% CI: -0.33 to 6.84); p-value= 0.08 FENO (<19.5 ppb): Least square mean difference= 1.97 (95% CI: -1.83 to 5.77); p-value= 0.31 Number of patients: 394; test for subgroup differences: P = 0.63 [c] 		⊕⊕◯◯ LOW	
Adverse events Follow up: 48 weeks (higher values, worst outcome)												
1 (394 participants)[1]	randomised trials	serious [a]	not serious	not serious	serious [b]	none	Percentage of patients with treatment-related adverse events of omalizumab compared to placebo were: FENO (≥19.5 ppb): 80.2% versus 73%; RR= 1.10 (95% CI= 0.94 to 1.28) FENO(<19.5 ppb): 83.5% versus 80%; RR= 1.04 (95% CI= 0.91 to 1.19) Number of patients: 394; test for subgroup differences: P=0.62 		⊕⊕◯◯ LOW	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	omalizumab	placebo	Relative (95% CI)	Absolute (95% CI)		
Time to first asthma exacerbation Follow up: 48 weeks (lower values, better outcome)												
1 (394 participants)[1]	randomised trials	serious [a]	not serious	not serious	serious [b]	none	Time to first asthma exacerbation of omalizumab compared to placebo were: FENO(≥19.5 ppb): HR= 0.38 (95% CI= 0.24 to 0.61) FENO(<19.5 ppb): HR= 1.0 (95% CI= 0.62 to 1.6) Number of patients: 394; test for subgroup differences: P=0.004 	⨁⨁◯◯ LOW	

CI: Confidence interval

Explanations

a. Risk of bias due to a considerable number of patients was not evaluated at baseline for biomarker levels

b. Optimal information size not reached for the main objective (and then for the subgroup analysis), reported by authors

c. P values about Test for subgroup differences were estimated in RevMan and assuming that LSM is similar to Mean differences (just for descriptive purposes)

References

1. Hanania NA1, Wenzel S,Rosén K,Hsieh HJ,Mosesova S,Choy DF,Lal P,Arron JR,Harris JM,Busse W. Exploring the effects of omalizumab in allergic asthma: an analysis of biomarkers in the EXTRA study. Am J Respir Crit Care Med; 2013.

Evidence to Decision Framework: OMALIZUMAB – PERIOSTIN

Should measurement of Periostin be used to select patients for initiation of a monoclonal anti-IgE strategy in adults and children with severe asthma?

POPULATION:	Adults and children (≥12 years) with severe asthma	**BACKGROUND:**	Until relatively recently treatment options for patients with severe asthma who were refractory to standard treatments have been limited. Over the last two decades there have been major advances in treatment options for patients with severe disease. In the early 2000s omalizumab, a monoclonal antibody therapy that targets and neutralises IgE entered the market. Since that time a number of other monoclonal antibody therapies targeting the T2 pathway have emerged. The treatments have proven efficacy in reducing exacerbations and oral corticosteroid requirements, and improving patient reported outcomes. With multiple treatment options now available it has become increasingly important to ensure that the right targeted treatment is delivered to the right patient with severe asthma. This approach allows for the delivery of personalised or precision medicine. It is now critical to understand the population in which targeted therapies are likely to have the greatest effect. Serum periostin does not appear useful in predicting reponse to anti-IgE treatment.
INTERVENTION:	Omalizumab compared to placebo in patients with severe asthma who have serum periostin levels ≥50 ng/ml		
COMPARISON:	Omalizumab in patients with severe asthma who have serum periostin levels <50 ng/ml		
MAIN OUTCOMES:	Exacerbation rates, time to first exacerbations, asthma related quality of life, FEV_1, adverse effects		

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ● **Trivial** ○ Small ○ Moderate ○ Large ○ Varies ○Don't know	Results from research evidence (studies) No differences were detected in terms of relative reduction of exacerbation rates at 48 weeks or FEV1 when omalizumab was compared to placebo in periostin high (50 ng/ml or more) or low (less than 50 ng/ml) patients. There were however improvements in baseline AQLQ scores with omalizumab compared to placebo in patients with low (less than 50 mg/ml) periostin levels at 48 weeks follow-up (MD 0.50 [0.22,0.78]), whereas there are no differences patients with high (50 ng/ml and more) periostin levels (MD 0.10 [-0.19,0.39]).	Panel considerations
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ● **Small** ○ Trivial ○ Varies ○ Don't know	There are no differences in terms adverse events at 48 weeks of follow-up, when omalizumab is compared to placebo in high or low periostin levels at baseline.	
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ○ Very low ● **Low** ○ Moderate ○ High ○ No included studies	The risk of bias was high for completeness of data, due to a considerable number of patients that were not evaluated at baseline for biomarker levels.	
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ● **Important uncertainty or variability** ○ Possibly important uncertainty or variability	The test -Serum Periostin: In a study which aimed to evaluate the patient perception of tests used for the assessment of asthma and COPD venipuncture had a reseasonabile assessment profile, it was rated as more painful that comparator tests eg. Questionaires but was acceptable in terms of comfort, difficulty and time taken to do the test[1].	

	○ Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes	The intervention did not lead to improvements in some outcomes that are valued by consumers in the biomarker high group, although there were larger quality of life improvements in the biomarker low group.	
BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ● **Does not favor either the intervention or the comparison** ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	There were no differences in terms of % predicted FEV1 mean change at 48 weeks of follow-up, when omalizumab is compared to placebo in high (50 ng/ml or more) or low (less than 50 ng/ml) periostin levels at baseline. There were no differenence in time to first asthma exacerbation with omalizumab compared to placebo in those patients with high (50 ng/ml or more) or low (less than 50 ng/ml) periostin levels at the same follow-up. In addition, there are no statistically significant differences between these subgroups Their were no differences in the adverse effects in patients treated with omalizumab versus placebo irrespective of high or low perisotin. There was a significant mean change of baselines AQLQ scores with omalizumab compared to placebo in those patients with low (less than 50 mg/ml) periostin levels at 48 weeks follow-up, whereas there were no differences in the same outcome for those patients with high (50 ng/ml and more) periostin levels at the same follow-up	
COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● **No included studies**	No research evidence identified.	There would be an additional cost of using Periostin.
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ○ Low ○ Moderate ○ High ● **No included studies**	No research evidence identified.	There would be an additional cost of using Periostin.

EQUITY	**What would be the impact on health equity?** ○ **Reduced** ○ Probably reduced ○ Probably no impact ○ Probably increased ●Increased ○ Varies ○ Don't know	No research evidence identified.	Perisotin is currently not available and is not applicable in children
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ● **No** ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence identified.	Periostin is currently only available for research and is not applicable to children. There is no evidence that periostin levels are useful in predicting exacerbation and lung function response to treatment.
FEASIBILITY	**Is the intervention feasible to implement?** ● **No** ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence identified.	At present periostin is only available in research setting and is not applicable to children.

Reference

1. McDonald VM, Simpson JL, McElduff P, Gibson PG. Older peoples' perception of tests used in the assessment and management of COPD and asthma. *Clin Respir J* 2013; **20**(10): 12017.

Evidence to Decision Framework: OMALIZUMAB – EOSINOPHILS

Should measurement of blood eosinophils be used to select patients for initiation of a monoclonal anti-IgE strategy in adults and children with severe asthma?

POPULATION:	Adults and children (≥12 years) with severe asthma
INTERVENTION:	Measurement of blood eosinophil counts and treatment with Omalizumab in patients with severe asthma who have ≥260/µl
COMPARISON:	Measurement of blood eosinophil counts and treatment with Omalizumab in patients with severe asthma who have <260/µl
MAIN OUTCOMES:	Exacerbation rates, time to first exacerbations, asthma related quality of life, FEV_1, adverse effects

BACKGROUND:

Until relatively recently treatment options for patients with severe asthma who were refractory to standard treatments have been limited. Over the last two decades there have been major advances in treatment options for patients with severe disease. In the early 2000s omalizumab, a monoclonal antibody therapy that targets and neutralises IgE entered the market. Since that time a number of other monoclonal antibody therapies targeting the T2 pathway have emerged. The treatments have proven efficacy in reducing exacerbations and oral corticosteroid requirements, and improving patient reported outcomes. With multiple treatment options now available it has become increasingly important to ensure that the right targeted treatment is delivered to the right patient with severe asthma. This approach allows for the delivery of personalised or precision medicine. It is now critical to understand the population in which targeted therapies are likely to have the greatest effect. An elevation of peripheral blood eosinophils can be used as a biomarker to predict reponse to anti-IgE treatment and enable this personalised approach.

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ○ Small ○ Moderate ● **Large** ○ Varies ○Don't know	Results from research evidence (studies) Included in the evidence synthesis were two randomised contolled trials. Pooling of the studies was not possible. In one study[1] using there were improvements in exacerbations rates (HR 0.41 [0.20, 0.84]) and a small but significantly greater change in FEV1 predicted at 24 weeks (MD 7.35 [1.38, 13.32]) with omalizumab compared to placebo in patients with a high eosinophil count (≥300/µl), whereas there were no differences in patients with low eosinophils (< 300/uL). In another RCT[2] there was a significantly longer time to first asthma exacerbation with omalizumab compared to placebo in patients with high (260/uL or more) eosinophil count at 48 weeks follow-up (HR 0.64 [0.48. 0.85]), whereas there were no differences in patients with low (less than 260/uL) eosinophil count (HR 0.95 [0.68, 1.33]). However, there were no statistically significant differences between these subgroups. There were no differences in terms of percentage of treatment-related adverse events at 48 weeks of follow-up, when omalizumab is compared to placebo in patients with high or low blood eosinophils. Undergoing a test for peripheral blood eosinophils involves venepuncture which may be more painful than not having a blood test, as such there may be small undesirable effects of the test.	Panel considerations
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ● **Small** ○ Trivial ○ Varies ○ Don't know		
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ○ Very low ● **Low** ○ Moderate ○ High ○ No included studies	The risk of bias was high for completeness of data, due to a considerable number of patients that were not evaluated at baseline for blood eosinophils.	
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ● Possibly important uncertainty or variability	The test - peripheral blood eosinophils: In a study which aimed to evaluate the patient perception of tests used for the assessment of asthma and COPD, venipuncture had a reseasonable assessment profile, it was rated as more painful than the comparator tests eg. Questionaires, but was acceptable in terms of comfort, difficulty and time taken to do the test[3].	

	○ **Probably no important uncertainty or variability** ○ No important uncertainty or variability ○ No known undesirable outcomes	The intervention led to improvements in outcomes that are highly valued by the consumer, as rated by the representatives on the Taskforce. In a study in severe asthma evaluating which outcomes matter to patients, reduced exacerbations and improved quality of life were viewed amongst their highest priorities (Clark V et. al, TSANZ 2019).	
BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● **Favors the intervention** ○ Varies ○ Don't know	People in the high and low eosinophil groups both experienced adverse effects, with no differences according to their subgroups. People in the eosinophil high group received the clinical benefit without any in increase side effects, whereas the low eosinophil group experienced the same side effects without the clinical benefit.	
COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● **Favors the intervention** ○ Varies ○ No included studies	No research evidence identified.	The intervention (measurement of eosinophils in the blood) is a low cost intervention that is already routinely used in practice in this population.
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ○ Low ● **Moderate** ○ High ○No included studies	No research evidence identified.	While no studies evaluated the evidence of resource requirements the certainty is high as blood eosinophil counts are a low cost test already used in most areas of medicine, as the biomarker is included in the full blood count.
EQUITY	**What would be the impact on health equity?**	No research evidence identified.	The measurement of peripherial blood eosinophil counts is low cost and readily

	○ Reduced ○ Probably reduced ● **Probably no impact** ○ Probably increased ○ Increased ○ Varies ○ Don't know		accessible, so all patients are likely to have the biomarker measured.
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ○ Probably yes ● **Yes** ○ Varies ○ Don't know	No research evidence identified.	The test is already available as a standard medical assessment at a low cost, so the use of this biomarker should not disadvantage any minority groups.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ○ Probably yes ● **Yes** ○ Varies ○ Don't know	No research evidence identified.	There are likely to be few limitations since this test is already freely available, low cost, already used in practice and generally acceptable to patients[3].

Reference

1. Busse W, Spector S, Rosen K, Wang Y, Alpan O. High eosinophil count: a potential biomarker for assessing successful omalizumab treatment effects. *The Journal of allergy and clinical immunology* 2013; **132**(2): 485-6.e11.

2. Hanania NA, Wenzel S, Rosen K, et al. Exploring the effects of omalizumab in allergic asthma: an analysis of biomarkers in the EXTRA study. *American journal of respiratory and critical care medicine* 2013; **187**(8): 804-11.

3. McDonald VM, Simpson JL, McElduff P, Gibson PG. Older peoples' perception of tests used in the assessment and management of COPD and asthma. *Clin Respir J* 2013; **20**(10): 12017.

Evidence to Decision Framework: OMALIZUMAB – FeNO

Should measurement of exhaled NO be used to select patients for initiation of a monoclonal anti-IgE strategy in adults and children with severe asthma?

POPULATION:	Adults and children (≥12 years) with severe asthma	**BACKGROUND:**	Until relatively recently treatment options for patients with severe asthma who were refractory to standard treatments have been limited. Over the last two decades there have been major advances in treatment options for patients with severe disease. In the early 2000s omalizumab, a monoclonal antibody therapy that targets and neutralises IgE entered the market. Since that time a number of other monoclonal antibody therapies targeting the T2 pathway have emerged. The treatments have proven efficacy in reducing exacerbations and oral corticosteroid requirements, and improving patient reported outcomes. With multiple treatment options now available it has become increasingly important to ensure that the right targeted treatment is delivered to the right patient with severe asthma. This approach allows for the delivery of personalised or precision medicine. It is now critical to understand the population in which targeted therapies are likely to have the greatest effect. An elevation of FeNO ≥19.5 ppb can be used as a biomarker to predict reponse to anti-IgE treatment and enable this personalised approach.
INTERVENTION:	Omalizumab compared to placebo in FeNO high (≥19.5 ppb) patients with severe asthma		
COMPARISON:	Omalizumab compared to placebo in FeNO high (<19.5 ppb) patients with severe asthma		
MAIN OUTCOMES:	Exacerbation rates, time to first exacerbations, asthma related quality of life, FEV_1, adverse effects		

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ○ Small ○ Moderate ● **Large** ○ Varies ○Don't know	Results from research evidence (studies) Only one RCT was included in this evidence systhesis There was a significant relative reduction of exacerbation rates with omalizumab compared to placebo in patients with high (19.5 ppb or more) FENO level at 48 weeks follow-up (53% [95% CI 37-70]); p=0.001, whereas there were no differences for those patients with low (less than 19.5 ppb) FENO levels (16% [95% CI: -32 to 46]); p= 0.45. The time to first asthma exacerbation with omalizumab compared to placebo was significantly longer in patients with high (19.5 ppb or more) FENO level at 48 weeks follow-up (HR 0.38 [0.24, 0.60]), whereas there were no differences in patients with low (less than 19.5 ppb) FENO (HR 1.00 [0.62, 1.61]). There were also larger changes of mean AQLQ with omalizumab compared to placebo in FeNO high patients (19.5 ppb or more) at 48 weeks of follow-up (MD 0.39 [0.06, 0.72]), whereas there were no differences in FeNO low patients (less than 19.5 ppb) (MD 0.24 [-0.09, 0.57]).	
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	Only one RCT was included in this evidence systhesis	There are no differences in terms of percentage of treatment-related adverse events at 48 weeks of follow-up, when omalizumab is compared to placebo in high or low FENO levels at baseline.

CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ○ Very low ● Low ○ Moderate ○ High ○ No included studies	The risk of bias was high for completeness of data, due to a considerable number of patients that were not evaluated at baseline for their FeNO level.	Each analysis only included single RCTs of patients with severe asthma eligible for anti-IgE treatment.
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ● **Possibly important uncertainty or variability** ○ Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes	The test - FeNO: In a study which aimed to evaluate the patient perception of tests used for the assessment of asthma and COPD, FeNO had a good assessment profile, with a favourable assessment overall compared to completing questionnaires and only being associated with some difficulty in test performance[1]. The intervention lead to improvements in outcomes that are highly valued by the consumer, as rated by the representatives on this Taskforce. In a study in severe asthma evaluating which outcomes matter to patients, reduced exacerbations and improved quality of life were viewed amongst their highest priorities (Clark V *etal*, TSANZ 2019).	
BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● **Favors the intervention** ○ Varies ○ Don't know		Their were no differences in the adverse effects in patients treated with omalizumab versus placebo irrespective of high or low FeNO. People in the FeNO high group received the clinical benenfit without any increase in side effects, whereas the low FeNO group experienced the same side effects without the clinical benefit.
COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● **No included studies**	No research evidence identified.	There would be an additional cost of using FeNO to select patients for the treatment in non specialist centres. However, in specialist centres FeNO is commonly assessed. If the test is used to select patients most likely to respond, cost benefits are likely.

CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ○ Low ○ Moderate ○ High ● **No included studies**	No research evidence identified.	Cost of the test may limit widescale implementation.
EQUITY	**What would be the impact on health equity?** ○ Reduced ● **Probably reduced** ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence identified.	There is no evidence of an impact on health equity, however given the lack of widespread FeNO use, some groups may not have access to the test.
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ● **Probably yes** ○ Yes ○ Varies ○ Don't know	Previous ERS/ATS Taskforce recommends against the use of FeNO to guide therapy of adults and children with severe asthma. This may impact acceptability[2]. In terms of patient acceptability, a study which aimed to evaluate the patient perception of tests used for the assessment of asthma and COPD, found that FENO had a good assessment profile, with a favourable assessment overall compared to completing questionnaires, and only being associated with some difficulty in test performance[1].	As treatment of omalizumab is initiated in specialist severe asthma clinics and FeNO is a common measure used in these clinics, it is likely that this is acceptable to severe asthma clinicians.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ● **Probably yes** ○ Yes ○ Varies ○ Don't know	No research evidence identified.	Cost of the test may limit widescale implementation.

References

1. McDonald VM, Simpson JL, McElduff P, Gibson PG. Older peoples' perception of tests used in the assessment and management of COPD and asthma. *Clin Respir J* 2013; **20**(10): 12017.

2. Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *The European respiratory journal* 2014; (43): 343-73.

Should a long-acting inhaled muscarinic antagonist (LAMA) be used in adults and children with severe asthma?

GRADE Evidence Profile: LAMA (tiotropium)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LAMA (tiotropium)	placebo	Relative (95% CI)	Absolute (95% CI)		
Peak FEV1 response - Children 2.5 ug												
1 [1]	randomised trials	serious [a]	not serious	not serious	not serious	none	135	130	MD **35 higher** (27.99 lower to 97.99 higher)		⊕⊕⊕◯ MODERATE	CRITICAL
Peak FEV1 response - Adolescents 2.5 ug												
1 [2]	randomised trials	not serious	not serious	not serious	serious [b]	none	127	135	MD **111 higher** (2.01 higher to 219.99 higher)		⊕⊕⊕◯ MODERATE	CRITICAL
Peak FEV1 response - Children 5 ug												
1 [1]	randomised trials	not serious	not serious	not serious	serious [b]	none	128	130	MD **139 higher** (74.32 higher to 203.68 higher)		⊕⊕⊕◯ MODERATE	CRITICAL
Peak FEV1 response - Adolescents 5 ug												
1 [2]	randomised trials	not serious	not serious	not serious	serious [b]	none	130	135	MD **90 higher** (18.99 lower to 198.99 higher)		⊕⊕⊕◯ MODERATE	CRITICAL
Peak FEV1 response - Adults 5 ug												
2 [3,4]	randomised trials	not serious	not serious	not serious	serious [b]	none	456	456	MD **120.74 higher** (54.12 higher to 187.36 higher)		⊕⊕⊕◯ MODERATE	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LAMA (tiotropium)	placebo	Relative (95% CI)	Absolute (95% CI)		
Change in ACQ-7 scores - Children 2.5 ug												
1[1]	randomised trials	not serious	not serious	not serious	not serious	none	136	130	MD **0.02 higher** (0.14 lower to 0.18 higher)		⊕⊕⊕⊕ HIGH	CRITICAL
Change in ACQ-7 scores - Adolescents 2.5 ug												
1[2]	randomised trials	not serious	not serious	not serious	not serious	none	127	135	MD **0.06 higher** (0.1 lower to 0.22 higher)		⊕⊕⊕⊕ HIGH	CRITICAL
Change in ACQ-7 scores - Children 5 ug												
1[1]	randomised trials	not serious	not serious	not serious	not serious	none	126	130	MD **0.08 lower** (0.24 lower to 0.08 higher)		⊕⊕⊕⊕ HIGH	CRITICAL
Change in ACQ-7 scores - Adolescents 5 ug												
1[2]	randomised trials	not serious	not serious	not serious	not serious	none	130	135	MD **0.04 higher** (0.12 lower to 0.19 higher)		⊕⊕⊕⊕ HIGH	CRITICAL
Change in ACQ-7 scores - Adults 5 ug												
2[3,4]	randomised trials	not serious	not serious	not serious	not serious	none	456	456	MD **0.17 lower** (0.25 lower to 0.09 lower)		⊕⊕⊕⊕ HIGH	CRITICAL
Asthma worsening (at least 1) - Children 2.5 ug												
1[1]	randomised trials	not serious	not serious	not serious	serious [c]	none	29/135 (21.5%)	23/65 (35.4%)	**RR 0.61** (0.38 to 0.96)	**138 fewer per 1.000** (from 219 fewer to 14 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LAMA (tiotropium)	placebo	Relative (95% CI)	Absolute (95% CI)		
Asthma worsening (at least 1) - Adolescents 2.5 ug												
1 [2]	randomised trials	not serious	not serious	not serious	serious [c]	none	18/127 (14.2%)	12/67 (17.9%)	**RR 0.79** (0.41 to 1.54)	**38 fewer per 1.000** (from 106 fewer to 97 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Asthma worsening (at least 1) - Children 5 ug												
1 [1]	randomised trials	not serious	not serious	not serious	serious [c]	none	35/128 (27.3%)	23/65 (35.4%)	**RR 0.77** (0.50 to 1.19)	**81 fewer per 1.000** (from 177 fewer to 67 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Asthma worsening (at least 1) - Adolescents 5 ug												
1 [2]	randomised trials	not serious	not serious	not serious	serious [c]	none	15/130 (11.5%)	12/67 (17.9%)	**RR 0.64** (0.32 to 1.30)	**64 fewer per 1.000** (from 122 fewer to 54 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Asthma worsening (at least 1) - Adults 5 ug												
1 [4]	randomised trials	not serious	not serious	not serious	not serious	none	226/453 (49.9%)	287/454 (63.2%)	**RR 0.79** (0.70 to 0.89)	**133 fewer per 1.000** (from 190 fewer to 70 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Peak FEV1 % predicted - Children 2.5 ug												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LAMA (tiotropium)	placebo	Relative (95% CI)	Absolute (95% CI)		
1 [1]	randomised trials	serious [a]	not serious	not serious	not serious	none	135	130	MD **3.6 higher** (0.5 higher to 6.7 higher)		⊕⊕⊕◯ MODERATE	IMPORTANT

Peak FEV1 % predicted - Children 5 ug

1 [1]	randomised trials	serious [a]	not serious	not serious	not serious	none	128	130	MD **6.3 higher** (3.3 higher to 9.3 higher)		⊕⊕⊕◯ MODERATE	IMPORTANT

Peak FEV1 % predicted - Children 5 ug

1 [1]	randomised trials	serious [a]	not serious	not serious	very serious[c]	none	Narrative report + figure: " Post hoc analyses of adjusted mean trough FEV1/FVC responses demonstrated statistically significant improvements at all-time points versus placebo with both tiotropium doses, with the exception of tiotropium 2.5 mg at week 8"				⊕⊕◯◯ LOW	IMPORTANT

Peak FEV1 % predicted - Children 5 ug

1 [1]	randomised trials	serious [a]	not serious	not serious	very serious[c]	none	Narrative report + figure: " Post hoc analyses of adjusted mean trough FEV1/FVC responses demonstrated statistically significant improvements at all-time points versus placebo with both tiotropium doses, with the exception of tiotropium 2.5 mg at week 8"				⊕⊕◯◯ LOW	IMPORTANT

AQLQ scores - Adults 5 ug

2 [3,4]	randomised trials	not serious	not serious	not serious	not serious	none	456	456	MD **0.1 higher** (0.04 lower to 0.23 higher)		⊕⊕⊕⊕ HIGH	CRITICAL

Time to first exacerbation - Adults 5 ug

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LAMA (tiotropium)	placebo	Relative (95% CI)	Absolute (95% CI)		
1 [4]	randomised trials	not serious	not serious	not serious	serious [d]	none	-/456	-/456	**HR 0.79** (0.62 to 1.01)		⊕⊕⊕◯ MODERATE	CRITICAL

Hospitalizations for asthma - Adults 5 ug

1 [4]	randomised trials	not serious	not serious	not serious	serious [c]	none	16/453 (3.5%)	20/454 (4.4%)	**RR 0.80** (0.42 to 1.53)	**9 fewer per 1.000** (from 26 fewer to 23 more)	⊕⊕⊕◯ MODERATE	IMPORTANT

Any adverse event - Children 2.5 ug

1 [1]	randomised trials	not serious	not serious	not serious	serious [c]	none	59/136 (43.4%)	33/67 (49.3%)	**RR 0.88** (0.65 to 1.20)	**59 fewer per 1.000** (from 172 fewer to 99 more)	⊕⊕⊕◯ MODERATE	CRITICAL

Any adverse event - Adolescents 2.5 ug

1 [2]	randomised trials	not serious	not serious	not serious	serious [c]	none	42/127 (33.1%)	24/68 (35.3%)	**RR 0.94** (0.62 to 1.41)	**21 fewer per 1.000** (from 134 fewer to 145 more)	⊕⊕⊕◯ MODERATE	CRITICAL

Any adverse event - Children 5 ug

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LAMA (tiotropium)	placebo	Relative (95% CI)	Absolute (95% CI)		
1 [1]	randomised trials	not serious	not serious	not serious	serious [c]	none	56/130 (43.1%)	33/67 (49.3%)	**RR 0.87** (0.64 to 1.20)	**64 fewer per 1.000** (from 177 fewer to 99 more)	⊕⊕⊕◯ MODERATE	CRITICAL

Any adverse event - Adolescents 5 ug

1 [2]	randomised trials	not serious	not serious	not serious	serious [c]	none	43/130 (33.1%)	24/68 (35.3%)	**RR 0.94** (0.63 to 1.40)	**21 fewer per 1.000** (from 131 fewer to 141 more)	⊕⊕⊕◯ MODERATE	CRITICAL

Any adverse event - Adults 5 ug

2 [3,4]	randomised trials	not serious	not serious	not serious	not serious	none	335/456 (73.5%)	366/456 (80.3%)	**RR 0.92** (0.86 to 0.98)	**64 fewer per 1.000** (from 112 fewer to 16 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL

Serious adverse events - Children 2.5 ug

1 [1]	randomised trials	not serious	not serious	not serious	very serious [c]	none	2/136 (1.5%)	1/67 (1.5%)	**RR 0.99** (0.09 to 10.67)	**0 fewer per 1.000** (from 14 fewer to 144 more)	⊕⊕◯◯ LOW	IMPORTANT

Serious adverse events - Adolescents 2.5 ug

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LAMA (tiotropium)	placebo	Relative (95% CI)	Absolute (95% CI)		
1 [2]	randomised trials	not serious	not serious	not serious	very serious [c]	none	0/127 (0.0%)	0/68 (0.0%)	not estimable		⊕⊕◯◯ LOW	IMPORTANT

Serious adverse events - Children 5 ug

1 [1]	randomised trials	not serious	not serious	not serious	very serious [c]	none	4/130 (3.1%)	1/67 (1.5%)	**RR 2.06** (0.24 to 18.08)	**16 more per 1.000** (from 11 fewer to 255 more)	⊕⊕◯◯ LOW	IMPORTANT

Serious adverse events - Adolescents 5 ug

1 [2]	randomised trials	not serious	not serious	not serious	very serious [c]	none	3/130 (2.3%)	0/68 (0.0%)	**RR 3.69** (0.19 to 70.36)	**0 fewer per 1.000** (from 0 fewer to 0 fewer)	⊕⊕◯◯ LOW	IMPORTANT

Serious adverse events - Adults 5 ug

2 [3,4]	randomised trials	not serious	not serious	not serious	serious [c]	none	37/456 (8.1%)	40/456 (8.8%)	**RR 0.93** (0.61 to 1.43)	**6 fewer per 1.000** (from 34 fewer to 38 more)	⊕⊕⊕◯ MODERATE	IMPORTANT

CI: Confidence interval; **MD:** Mean difference; **SMD:** Standardised mean difference; **RR:** Risk ratio; **HR:** Hazard Ratio

Explanations

a. Selective reporting bias: Some outcomes were assessed post-hoc including peak FEV1 (0-3h)

b. Although we cannot exclude futility because all estimates do not reach MID, upper 95% CI boundary is next to clinically important effect. Minimal important differences for FEV1 change= 230 millilitres

c. Small number of events, large 95%CI

d. Large 95CI% which includes no effect or a relevant benefit

References

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3. Kerstjens HA, Moroni-Zentgraf P,Tashkin DP,Dahl R,Paggiaro P,Vandewalker M,Schmidt H,Engel M,Bateman ED.. Tiotropium improves lung function, exacerbation rate, and asthma control, independent of baseline characteristics including age, degree of airway obstruction, and allergic statu. Respir Med; 2016.
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Evidence to Decision Framework: LAMA (tiotropium)

Should **tiotropium** vs. **no tiotropium** be used for **children, adolescents, and adults with severe asthma uncontrolled despite GINA step 4-5 or NAEPP step 5 therapies**?

POPULATION:	Patients with severe asthma not controlled or experiencing exacerbations despite treatment with high-dose inhaled glucocorticoids in combination with a long-acting beta2-adrenergic receptor agonist and a third controller such as a leukotriene modifier if the patient is treated with medium-dose inhaled glucocorticoids.
INTERVENTION:	Muscarinic antagonist therapy with tiotropium via soft-mist inhaler (5ug or 10ug) once daily. Tiotropium 2.5ug or 5ug once daily was also evaluated in children and adolescents.
COMPARISON:	Placebo
MAIN OUTCOMES:	FEV1, PEFR, severe exacerbations, asthma symptoms, ACQ-7, ACQ-6, AQLQ

BACKGROUND:

. Several randomized clinical trials have demonstrated that the addition of a long-acting muscarinic antagonist as a second long-acting bronchodilator, initially in COPD, but more recently in mild to severe asthma cohorts, results in improvement in lung function and the prevention of exacerbations. Long-acting muscarinic antagonists such as tiotropium are the most frequently used long-acting bronchodilator for COPD and are a cost-effective and safe adjunct therapy for the management of asthma refractory to a combination of therapies which accounts for a substantial proportion of the burden related to asthma morbidity.

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ○ Small ○ Moderate ◙ Large ○ Varies ○Don't know	Results from research evidence (studies) There were three randomised placebo-controlled trials in adults greater than 18 years of age, one crossover and two parallel design, and two in either children or adolescents which impacted the dose of tiotropium (adults were randomized to 5 to 10ug while children and adolescents were randomized to 2.5-5ug once daily). All of these trials included individuals with severe asthma uncontrolled on GINA step 4-5 or NAEPP step 5 therapies. Each trial consistently demonstrated substantial and significant improvements in lung function measures and symptom control with the addition of tiotropium and a subgroup of sufficient duration demonstrated beneficial effects on time to exacerbation. Adverse events were less frequent in the tiotropium arm compared to placebo in these four trials, while severe adverse events were equally infrequent across treatment arms.	
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ○ Small ◙ Trivial ○ Varies ○ Don't know		
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ○ Very low ○ Low ◙ Moderate ○ High ○ No included studies	The five included studies were randomised, double-blind, placebo-controlled studies. All of the important primary and secondary outcomes were assessed as hiqh quality according to GRADE Overall risk of bias was low and methodological procedures for random sequence generation, allocation concealment, and blinding were robust. However, one 12-week study of children (Szefler 2017 [PMID:28189771]) may be subject to selective reporting bias as outcomes related to FEF-25-75%, peak and trough FEV1 responses at week 12, and time to exacerbation were assessed post-hoc but presented as main findings. Industry bias is also unclear in four of the five included.	
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ◙ Possibly important uncertainty or variability	There is value placed on the measurement of lung function and the management and prevention of asthma exacerbations. Lung function measures derived from spirometry are a fundamental measure of lung health, are highly correlated with asthma severity and exacerbation risk, and one of the central components determining asthma severity and NAEPP guideline-based maintenance treatment (Denlinger Am J Respir Crit Care Med.	

	○ Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes	2017;195(3):302-13. PMID:27556234). Asthma exacerbations account for much of the cost related to asthma (Weiss J Allergy Clin Immunol 2001 PMID:11149982). Exacerbations defined by the need for an intervention such as treatment with systemic glucocorticoids, an emergency room visit, or hospitalization is validated as one the central components for determining asthma severity and GINA/NAEPP guideline-based maintenance therapy (Fuhlbrigge J Allergy Clin Immunol 2012 PMID: 22386508).	
BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Long-acting muscarinic antagonist treatment was associated with substantial and significant improvements in peak lung function, symptom control, and a lower frequency of asthma worsening. There was a lower frequency of adverse events associated with tiotropium treatment while the frequency of severe adverse events was also low and nearly equal to placebo.	
COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies X No included studies	No cost-effectiveness analyses were identified.	Long-acting muscarinic antagonist therapy was associated with beneficial effects on asthma control, severe exacerbations, and lung function in those severe asthma treated with GINA step 4-5 or NAEPP step 5 therapies. Whether these costs savings outweigh the cost of medication is unclear, but the addition of this inhaled therapy can be done at a lower cost compared to biologic therapies.
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ○ Low ○ Moderate ○ High ● No included studies	No included studies.	

EQUITY	**What would be the impact on health equity?** ○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies X Don't know	Kerstjens and colleagues evaluated subgroups based on age, sex, ethnic and racial groups, and BMI/obesity and found equally beneficial effects on peak FEV1 improvement across sexes and individuals ages 18 or higher and less than 18 years (Kerjstens Respir Med 2016 [PMID:27492532]). This analysis was unable to determine whether there were equally beneficial effects racial groups such as African Americans (N=41), or Asians (N=93) who were the minority of subjects compared to Whites (N=714). In addition, effects were unable to be determined for Hispanic ethnicity (N=25) compared to non-Hispanics (N=826). An anticipated impact could relate to the access and lower cost of tiotropium when compared to biologic drugs which could impact health equity as it relates to socioeconomic status and the treatment of severe asthma.	
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no X Probably yes ○ Yes ○ Varies ○ Don't know	Long-acting muscarinic antagonist therapy improves FEV1 and prevents asthma worsening and exacerbations which may be important in this important subgroup of asthma who experience a substantial proportion of the burden related to asthma morbidity. An introduction of this feasible and cost-effective add-on therapy which effectively impacts these important outcomes is assumed to be highly acceptable to patients and healthcare providers.	
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no X Probably yes ○ Yes ○ Varies ○ Don't know	An inhaled therapy delivered once daily is a feasible intervention to implement in terms of convenience and ease of use. Feasibility could be limited by cost in individuals who are already treated with multiple inhaled therapies. Access to providers with sufficient expertise to add-on therapy above GINA step 4-5 or NAEPP step 5 therapies in these subgroups. In these settings, implementation of a once-daily inhaled device which could be used at home is substantially more feasible compared to more costly biologic therapies which are regularly administered in a clinic setting.	

Should a macrolide (i.e., azithromycin, clarithromycin) be used in adults and children with severe asthma?

Evidene Profile: MACROLIDES

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Macrolide	Placebo	Relative (95% CI)	Absolute (95% CI)		
Number of exacerbations requiring hospitalisation (follow up: mean 26 weeks)												
1 [1]	randomised trials	not serious	not serious	not serious	very serious [a,b]	none	2/55 (3.6%)	2/54 (3.7%)	**RR 0.98** (0.14 to 6.72)	**1 fewer per 1,000** (from 32 fewer to 212 more)	⨁⨁◯◯ LOW	CRITICAL
Number of 'severe' exacerbations - requiring at least oral corticosteroids (follow up: range 24 weeks to 48 weeks)												
3 [1-3]	randomised trials	not serious	serious [c]	not serious	serious [a]	none	72/285 (25.3%)	97/280 (34.6%)	**RR 0.77** (0.44 to 1.34)	**80 fewer per 1,000** (from 118 more to 194 fewer)	⨁⨁◯◯ LOW	CRITICAL
Incidence rate (moderate and severe combined) asthma exacerbations (follow up: mean 48 weeks)												
1 [2]	randomised trials	not serious	not serious	not serious		none	213	207	**Rate ratio 0.59** (0.47 to 0.74)	Incidence rate (events/patient/year): macrolides 1.07; placebo 1.86	-	CRITICAL
Number of patients with at least one moderate or severe asthma exacerbation (follow up: mean 48 weeks)												
1 [2]	randomised trials	not serious	not serious	not serious	not serious	none	94/213 (44.1%)	127/207 (61.4%)	**RR 0.72** (0.60 to 0.87)	**172 fewer per 1,000** (from 80 fewer to 245 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL
Time to asthma exacerbation (moderate or severe) (follow up: mean 48 weeks)												
1 [2]	randomised trials	not serious	not serious	not serious	not serious	none	94	127	**HR 0.65** (0.50 to 0.85)	-	⨁⨁⨁⨁ HIGH	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Macrolide	Placebo	Relative (95% CI)	Absolute (95% CI)		
Note: HR is 0.65 (95% CI up to 0.85) and the median difference (point estimate) almost 200 days which suggests that the HR reduction is substantial.												
Number of lower respiratory tract infections requiring antibiotics (follow up: range 26 weeks to 48 weeks)												
2 [1,2]	randomised trials	not serious	not serious	not serious	not serious	none	56/268 (20.9%)	93/261 (35.6%)	**RR 0.60** (0.45 to 0.79)	**143 fewer per 1,000** (from 75 fewer to 196 fewer)	⨁⨁⨁⨁ HIGH	
Note: Although exacerbations were designated to be of critical importance by the panel, it is not known how lower respiratory tract infections were considered therefore importance is left blank awaiting outcome of further discussion with the panel.												
Change in Asthma Control Questionnaire (ACQ) score from baseline (follow up: range 16 weeks to 48 weeks; Scale from: 0 to 7; MID 0.5)												
3 [1,4,5]	randomised trials	not serious	not serious	not serious	not serious	none	140	136	-	MD **0.11 lower** (0.34 lower to 0.12 higher)	⨁⨁⨁⨁ HIGH	CRITICAL
Post treatment ACQ score (follow up: range 8 weeks to 48 weeks; Scale from: 0 to 7; MID 0.5)												
2 [2,6]	randomised trials	not serious	not serious	not serious	not serious	none	236	229	-	MD **0.07 lower** (0.24 lower to 0.11 higher)	⨁⨁⨁⨁ HIGH	CRITICAL
Change in symptom score from baseline (follow up: mean 48 weeks; Scale from: 0 to 4)												
1 [4]	randomised trials	not serious	not serious	not serious	very serious [a,b]	none	38	37	-	MD **0.17 higher** (0.28 lower to 0.63 higher)	⨁⨁◯◯ LOW	CRITICAL
Post treatment total symptom score (follow up: mean 8 weeks; Scale from: 0 to 14)												
1 [6]	randomised trials	not serious	not serious	not serious	very serious [a,b]	none	23	22	-	MD **0.3 lower** (2.08 lower to 1.48 higher)	⨁⨁◯◯ LOW	CRITICAL
Mean end of treatment breathlessness score (Visual Analogue Score) (follow up: mean 48 weeks; Scale from: 0 to 10 cm; MID 1.9 cm)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Macrolide	Placebo	Relative (95% CI)	Absolute (95% CI)		
1 [2]	randomised trials	not serious	not serious	not serious	serious [a]	none	212	207	-	MD **0.49 lower** (1.18 lower to 0.2 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Mean end of treatment wheeze score (Visual Analogue Score) (follow up: mean 48 weeks; Scale from: 0 to 10 cm)												
1 [2]	randomised trials	not serious	not serious	not serious	serious [a]	none	212	207	-	MD **0.11 lower** (1.15 lower to 0.94 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Mean end of treatment sputum production score (Visual Analogue Score) (follow up: mean 48 weeks; Scale from: 0 to 10 cm)												
1 [2]	randomised trials	not serious	not serious	not serious	serious [f]	none	212	207	-	MD **0.62 lower** (1.23 lower to 0.002 lower)	⨁⨁⨁◯ MODERATE	CRITICAL
Mean end of treatment cough score (Visual Analogue Score) (follow up: mean 48 weeks; Scale from: 0 to 10 cm, MID 1.7 cm)												
1 [2]	randomised trials	not serious	not serious	not serious	serious [e]	none	212	207	-	MD **0.73 lower** (1.42 lower to 0.04 lower)	⨁⨁⨁◯ MODERATE	CRITICAL
Number of patients with at least 1 adverse effect (follow up: mean 26 weeks)												
1 [1]	randomised trials	not serious	not serious	not serious	very serious [a,b]	none	37/55 (67.3%)	39/54 (72.2%)	**RR 0.93** (0.73 to 1.19)	**51 fewer per 1,000** (from 137 more to 195 fewer)	⨁⨁◯◯ LOW	CRITICAL
Number of serious adverse events (including mortality) (follow up: range 16 weeks to 48 weeks)												
4 [1,2,4,5]	randomised trials	not serious	not serious	not serious	very serious [a,b]	none	32/353 (9.1%)	39/343 (11.4%)	**RR 0.81** (0.52 to 1.24)	**22 fewer per 1,000** (from 27 more to 55 fewer)	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Macrolide**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Number of withdrawals due to adverse events (follow up: range 16 weeks to 48 weeks)												
4 [1-4]	randomised trials	not serious	not serious	not serious	very serious [a,b]	none	17/323 (5.3%)	13/317 (4.1%)	**RR 1.28** (0.64 to 2.59)	**11 more per 1,000** (from 15 fewer to 65 more)	⨁⨁◯◯ LOW	CRITICAL
Note: Note that although serious adverse events were lower in the treatment group, there were more withdrawals due to adverse events, suggesting these results should be considered with low confidence.												
Change in Asthma Quality of Life Questionnaire (AQLQ) from baseline (follow up: range 16 weeks to 48 weeks; Scale from: 1 to 7, MID 0.5)												
3 [1,4,5]	randomised trials	not serious	not serious	not serious	not serious	none	140	136	-	MD **0.16 higher** (0.06 lower to 0.37 higher)	⨁⨁⨁⨁ HIGH	IMPORTANT
Mean end of treatment AQLQ score (follow up: mean 48 weeks; Scale from: 1 to 7, MID 0.5)												
1 [2]	randomised trials	not serious	not serious	not serious	serious [e]	none	209	204	-	MD **0.36 higher** (0.21 higher to 0.52 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT
Mean end of treatment nasal symptom score (Visual Analogue Score) (follow up: mean 48 weeks; Scale from: 0 to 10 cm; MID 2.3 cm)												
1 [2]	randomised trials	not serious	not serious	not serious	serious [e]	none	212	207	-	MD **0.51 lower** (1.04 lower to 0.02 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT
Change in post-bronchodilator FEV1 (% predicted) from baseline (follow up: mean 26 weeks; MID 10.38 %)												
1 [1]	randomised trials	not serious	not serious	not serious	serious [b]	none	55	54	-	MD **1.95 higher** (2.42 lower to 6.32 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT
Change in pre-bronchodilator FEV1 (% predicted) from baseline (follow up: range 16 weeks to 26 weeks; MID 10.38 %)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Macrolide**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
2 [1,5]	randomised trials	not serious	not serious	not serious	serious [b]	none	102	99	-	MD **0.37 higher** (2.17 lower to 2.91 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT
Change in pre-bronchodilator FEV1 (L) (follow up: mean 16 weeks; MID 0.23 L)												
1 [5]	randomised trials	not serious	not serious	not serious	serious [b]	none	47	45	-	MD **0** (0.2 lower to 0.2 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT
Mean end of treatment pre-bronchodilator FEV1 (% predicted) (follow up: mean 8 weeks; MID 10.38 %)												
1 [6]	randomised trials	not serious	not serious	not serious	very serious [a,b]	none	23	22	-	MD **5.6 higher** (5.62 lower to 16.82 higher)	⨁⨁◯◯ LOW	IMPORTANT
Mean end of treatment pre-bronchodilator FEV1 (L) (follow up: mean 48 weeks; MID 0.23 L)												
1 [2]	randomised trials	not serious	not serious	not serious	serious [e]	none	210	205	-	MD **0.12 lower** (0.27 lower to 0.03 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **HR:** Hazard Ratio; **MD:** Mean difference

Explanations

a. The ends of the 95% CI include both appreciable benefit and appreciable harm and would lead to opposite clinical decisions.

b. Limited number of patients or events, does not meet OIS

c. There is variation in point estimates for included studies with an I2 of 70% which may indicate moderate inconsistency

d. One study reports 'number of patients with at least one primary endpoint' which is a composite of severe asthma exacerbations and lower respiratory tract infections requiring antibiotics. This study contributes 42% of events. Inclusion of lower respiratory tract infections means this data cannot be considered completely representative of exacerbations alone.

e. The lower end of the 95% CI crosses the minimally important difference (MID) for this outcome.

f. MID not established for this measure however lower end of confidence interval (score 0.002 lower) unlikely to be clinically meaningful.

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Evidence to Decision Framework: MACROLIDES

Should a macrolide (i.e., azithromycin, clarithromycin) be used in adults and children with severe asthma?

POPULATION:	Adults and children with severe asthma
INTERVENTION:	Macrolide
COMPARISON:	No macrolide
MAIN OUTCOMES:	Rate of exacerbations Time to first asthma exacerbation Asthma exacerbations requiring ER visits or hospitalization Lung function Asthma control Maintenance corticosteroid dose reduction Adverse events Serious adverse events Quality of life

BACKGROUND:

By definition, patients with severe asthma have disease that is either unresponsive to traditional therapies with inhaled corticosteroids and bronchodilators or require these therapies to maintain adequate control. To address this unmet need for improved therapies, in particular in patients not responding to step 5 biologicals or having no access to those treatments, and in view of the possible immunomodulatory effect of macrolides, these medications are being used long-term for the management of the disease. This systematic review and meta-analysis synthetizes the data from randomized controlled trials and meta-analyses investigating the use of macrolides and provides treatment recommendations based on the results.

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ● Small ○ Moderate ○Large ○ Varies ○Don't know	We identified a total of 6 clinical trials assessing the effectiveness of macrolide treatment to placebo. Four assessed azithromycin (Bruselle 2013, Gibson 2017, Strunk 2008, Hahn 2012) and two assessed clarithromycin (Sutherland 2010, Simpson 2008). In the largest study to date (Gibson), azithromycin 500mg (three times/week during 48 weeks) reduced asthma moderate to severe exacerbations (1·07 per patient-year [95% CI 0·85-1·29]) compared with placebo (1·86 per patient-year [1·54-2·18]; incidence rate ratio [IRR] 0·59 [95% CI 0·47-0·74]) and time to moderate to severe exacerbation; hazard ratio [HR] 0·65 [95% CI 0·50-0·85]. The proportion of patients experiencing at least one asthma exacerbation was reduced by azithromycin treatment (127 [61%] patients in the placebo group vs 94 [44%] patients in the azithromycin group; rate ratio [RR] 0·72 [95% CI 0·60-0·87]). Azithromycin significantly improved asthma-related quality of life questionnaire (AQLQ) at the end of treatment (adjusted mean difference, 0·36 [95% CI 0·21-0·52]). Macrolides were not associated to a reduction of severe exacerbations (Bruselle 2013, Gibson 2017, Strunk 2008), improvements in asthma control questionnaire (ACQ) (Bruselle 2013, Gibson 2017, Strunk 2008, Hahn 2012, Sutherland 2010, Simpson 2008) or lung function (FEV1) (Bruselle 2013, Gibson 2017, Sutherland 2010, Simpson 2008). In the AZISAST trial, in a predefined subgroup with non-eosinophilic severe asthma (blood eosinophilia ≤200/µl), azithromycin was associated with a significantly lower combined primary endpoint rate* (PEP) than placebo in subjects: 0.44 PEPs (95% CI 0.25 to 0.78) versus 1.03 PEPs (95% CI 0.72 to 1.48) (p=0.013). Azithromycin significantly improved the AQLQ score but there were no significant between-group differences in the ACQ score or lung function In the small study by Sutherland et al. clarithromycin improved airway hyperresponsiveness, increasing the methacholine PC(20) by 1.2 ± 0.5 doubling doses (P = .02) in the study population but had no effect on other outcomes.. * PEP is a rate of "primary endpoints" which is a combined measure of effect of severe asthma exacerbations and LRTI requiring antibiotics	• Rate ratios are difficult to judge (as any relative measure of effect). However, the absolute difference in this study is -0.46 (-0.79 to -0.14) exacerbations per patient-year (Table 2 - primary outcomes). The panel can better consider if less 0.14 exacerbations per patient-year is something meaningful • One approach would be also the NNT (at one year) as 1/absolute difference which seems to be 2 (1 to 7). The absolute difference estimate is adjusted in the trial so this NNT seems reliable. The panel can also judge whether treating 7 patients with azithromycin to avoid one (moderate or severe) exacerbation a year is acceptable. • The panel have to consider that patients with exacerbations (as defined) will need increased doses of steroids, B-agonists, ED visits or hospitalisations

UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	There were no differences between macrolides and placebo in the number of patients with serious adverse events or treatment withdrawal due to toxicity (Bruselle 2013, Gibson 2017, Strunk 2008, Hahn 2012, Sutherland 2010). The main concern is resistance which has been shown to develop in long-term use of macrolides. In the Azistast study azithromycin was associated with increased oropharyngeal carriage of macrolide-resistant streptococci (87% of the subjects in the azithromycin group and 35% of the subjects in the placebo group were colonised with erythromycin-resistant oropharyngeal streptococci p<0.001). There are more data in the literature about macrolide resistance from studies in other diseases where the medication is used long-term, such as non-CF bronchiectasis, where Valery et al. showed increased resistance to streptococcus pneumoniae and staph aureus rising from 12% to 27% after long term use compared to placebo (p=0.015 and 0.046 respectively). Similar data were found in other studies.(Wong LANCET 2012, Altenburg JAMA 2013). Diarrhoea is the most common adverse event. In the AZISAST study 72 [34%] azithromycin-treated patients experienced diarrhea vs 39 [19%] of those on placebo p=0·001).	• This is the most important consideration. However studies in non CF bronchiectasis showed that these bacteria were susceptible to other antibiotics.
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ● Very low ● Low ○ Moderate ○ High ○ No included studies	As shown in the table by Sarah Diver, the certainty of the evidence is low.	Our certainty assessment relies on study design (randomized controlled trials), risk of bias, inconsistency, indirectness , and imprecision . Further the certainty is based on the quality of evidence that is lowest among critical outcomes.
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability ○ No known undesirable outcomes	No evidence identified.	There is no important uncertainty about how patients and clinicians assess asthma exacerbations. There is more variability concerning QoL which however is a patient related outcome. Regarding the interpretation of lung function which is more objective there doesn't seem to be any effect of macrolide treatment on lung function.

BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Diarrhea does not seem to be a major concern, however the problem of resistance needs to be evaluated long-term in actual clinical studies (not only laboratory testing).	The group placed a higher value on the potential benefit of reduction in exacerbations which can be life-threating and the potential positive impact in quality of life. Potential adverse events were considered to have a lower value. Regarding resistance in particular, which is a concern, the studies show that the bacteria are susceptible to other commonly used antibiotics .
COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ No included studies	If, as the statistician points out, 7 patients need to be treated to avoid 1 exacerbation then probably the cost-effectiveness favors the intervention as the cost of the intervention is low while direct/indirect costs of exacerbations are high	No cost-effectiveness studies have been identified however the impact of asthma exacerbations on health care costs among patients with moderate and severe persistent asthma are estimated to be 9,223 USD compared to 5,011 USD in those asthmatic patients without exacerbations (Ivanova 2012). The estimated total healthcare cost of patients with exacerbations is 4,212 USD per year. Considering that macrolides are low-cost interventions, the panel considers that the intervention will be cost-saving.
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ○ Low ○ Moderate ○ High ● No included studies	No specific studies were identified, however due to the relatively low cost of macrolides resource requirements are expected to be low.	
EQUITY	**What would be the impact on health equity?** ○ Reduced ○ Probably reduced ○ Probably no impact	No evidence identified.	In the US, racial and ethnic minorities, and individuals of lower socioeconomic status have been documented to have less access to specialty clinics and are less likely to use expensive controller therapy for asthma. Macrolides might be an easy and feasible strategy.

	● Probably increased ○ Increased ○ Varies ○ Don't know		
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	No evidence identified.	Most patients with severe asthma welcome any possibility of improvement through treatment although they are concerned about medication use Health insurance companies and clinic administrations should find macrolides acceptable due to their relatively low cost however there is concern about the resistance.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Probably yes.	Macrolides are relatively cheap and are available world-wide. .

Should an anti-interleukin 4/13 strategy be used for adults and children with severe asthma?

Evidence Profile:300 mg of dupilumab every 2 weeks compared to placebo for patients with severe asthma according to blood eosinophils

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Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	300 mg of dupilumab every 2 weeks	placebo	Relative (95% CI)	Absolute (95% CI)		
EXACERBATION - annualised severe exacerbation event rate at week 24 (according to blood eosinophil 300 cells/mm3 or more)												
2 [1,2]	randomised trials	serious [a]	not serious	not serious	not serious	none	-/109	-/112	**Rate ratio 0.25** (0.14 to 0.46)	**Low** **84 less severe exacerbations per 100 patients per year** (from 49 to 139) **High** **124 less severe exacerbations per 100 patients per year** (from 94 to 155)	⊕⊕⊕◯ MODERATE	
EXACERBATION - annualised severe exacerbation event rate at week 24 (according to blood eosinophil <300 cells/mm3)												
2 [1,2]	randomised trials	serious [a]	not serious	not serious	not serious	none	0/156	0/148	**Rate ratio 0.49** (0.31 to 0.76)	**Low** **47 less severe exacerbations per 100 patients per year** (from 32 to 65) **High**	⊕⊕⊕◯ MODERATE	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	300 mg of dupilumab every 2 weeks	placebo	Relative (95% CI)	Absolute (95% CI)		
										66 less severe exacerbations per 100 patients per year (from 54 to 76)		
LUNG FUNCTION - change in FEV1 from baseline at week 24 (according to blood eosinophil 300 cells/mm3 or more) (assessed with: Liters)												
2 [1,2]	randomised trials	serious [a]	not serious	not serious	serious [b]	none	103	91	-	least square MD **0.21 Liters more** (0.06 more to 0.35 more)	⊕⊕◯◯ LOW	
LUNG FUNCTION - change in FEV1 from baseline at week 24 (according to blood eosinophil <300 cells/mm3) (assessed with: Liters)												
2 [1,2]	randomised trials	serious [a]	not serious	not serious	not serious	none	137	138	-	least square MD **0.14 Liters more** (0.05 more to 0.22 more)	⊕⊕⊕◯ MODERATE	
LUNG FUNCTION - change in FEV1 from baseline at week 24 (according to blood eosinophil 300 cells/mm3 or more) (assessed with: % of change; Scale from: 0 to 100)												
1 [1]	randomised trials	serious [c]	not serious	not serious	serious [d]	none	58	52	-	least square MD **12.09 percentage points more** (3.2 more to 20.97 more)	⊕⊕◯◯ LOW	
LUNG FUNCTION - change in FEV1 from baseline at week 24 (according to blood eosinophil <300 cells/mm3) (assessed with: % of change; Scale from: 0 to 100)												
1 [1]	randomised trials	serious [c]	not serious	not serious	serious [d]	none	85	73	-	least square MD **7.9 percentage points more** (1.98 more to 13.81 more)	⊕⊕◯◯ LOW	
ASTHMA CONTROL - at week 24 according to blood eosinophil 300 cells/mm3 or more (assessed with: ACQ-5; Scale from: 0 to 6)[e]												
1 [1]	randomised trials	serious [c]	not serious [f]	not serious	serious [b]	none	58	52	-	least square MD **0.55 ACQ-5 units lower** (0.9 lower to 0.2 lower)	⊕⊕◯◯ LOW	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	300 mg of dupilumab every 2 weeks	placebo	Relative (95% CI)	Absolute (95% CI)		
ASTHMA CONTROL - at week 24 according to blood eosinophil <300 cells/mm3 (assessed with: ACQ-5; Scale from: 0 to 6)[e]												
1 [1]	randomised trials	serious [c]	not serious [f]	not serious	not serious	none	87	75	-	least square MD **0.17 ACQ-5 units lower** (0.44 lower to 0.1 higher)	⊕⊕⊕◯ MODERATE	
QUALITY OF LIFE - at week 24 according to blood eosinophil 300 cells/mm3 or more (assessed with: AQLQ ; Scale from: 0 to 7)[g]												
1 [1]	randomised trials	serious [c]	not serious [f]	not serious	serious [b]	none	56	53	-	least square MD **0.78 AQLQ units higher** (0.42 higher to 1.15 higher)	⊕⊕◯◯ LOW	
QUALITY OF LIFE - at week 24 according to blood eosinophil <300 cells/mm3 (assessed with: AQLQ; Scale from: 0 to 7)[g]												
1 [1]	randomised trials	serious [c]	not serious [f]	not serious	not serious	none	85	74	-	least square MD **0.06 AQLQ units higher** (0.24 lower to 0.36 higher)	⊕⊕⊕◯ MODERATE	
Reduction in the glucocorticoid dose at week 24 (according to blood eosinophil 300 cells/mm3 or more) (assessed with: % reduction; Scale from: 0 to 100)												
1 [2]	randomised trials	serious [h]	not serious [f]	not serious	serious [i]	none	48	41	-	least square MD **36.38 percentage points lower** (54.7 lower to 18.9 lower)	⊕⊕◯◯ LOW	
Reduction in the glucocorticoid dose at week 24 (according to blood eosinophil <300 cells/mm3) (Scale from: 0 to 100)												
1 [2]	randomised trials	serious [h]	not serious [f]	not serious	serious [i]	none	55	66	-	least square MD **21.3 percentage points lower** (38.8 lower to 3.9 lower)	⊕⊕◯◯ LOW	

CI: Confidence interval

Explanations

a. Relevant and differential attrition bias in NCT01854047 (Wenzel 2016) for placebo and dupilumab groups (more than 20% and around 10% respectively); Randomization was not stratified by blood eosinophil count and current 300 cells/mm3 was not included as a co-variate in the analysis (Rabe 2018)
b. the lower CI boundary crosses the threshold for minimal important difference
c. Relevant and differential attrition bias in NCT01854047 (Wenzel 2016) for placebo and dupilumab groups (more than 20% and around 10% respectively)
d. Minimal important differences not known for % reduction in the FEV1, however the 95CI is wide and does not exclude important benefit or no effect.
e. minimal important difference for ACQ-5 is 0.5; lower values indicate better asthma control.
f. not applicable (findings from 1 trial)
g. minimal important difference for AQLQ is 0.5; higher scores indicates better QoL.
h. Subgroup analysis, randomization was not stratified by blood eosinophil count and current 300 cells/mm3 was not included as a co-variate in the analysis.
i. Minimal important differences not known for % reduction in the glucocorticoid doses, however the 95CI is wide and does not exclude important benefit or no effect.

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Evidence Profile: 300 mg of dupilumab every 2 weeks compared to placebo for patients with uncontrolled asthma

Bibliography: Castro M, Corren J, Pavord ID, Maspero J, Wenzel S, Rabe KF, Busse WW, Ford L, Sher L, FitzGerald JM, Katelaris C, Tohda Y, Zhang B, Staudinger H, Pirozzi G, Amin N, Ruddy M, Akinlade B, Khan A, Chao J, Martincova R, Graham NMH, Hamilton JD, Swanson BN, Stahl N, Yancopoulos GD, Teper A. Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma. N Engl J Med. 2018;378(26):2486-2496. doi: 10.1056/NEJMoa1804092. Wenzel S, Castro M, Corren J, Maspero J, Wang L, Zhang B, Pirozzi G, Sutherland ER, Evans RR, Joish VN, Eckert L, Graham NM, Stahl N, Yancopoulos GD, Louis-Tisserand M, Teper A. Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting β2 agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial. Lancet. 2016;388(10039):31-44. doi: 10.1016/S0140-6736(16)30307-5.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	300 mg of dupilumab every 2 weeks	placebo	Relative (95% CI)	Absolute (95% CI)		
EXACERBATION - annualised severe exacerbation event rate (dupilumab during 24 weeks)												
1	randomised trials	serious [a]	not serious [b]	not serious	not serious	none	NCT01854047 (Wenzel 2016) reported a risk reduction in event rates of 70·5% (45·4 to 84·1) in favour of 24 weeks of treatment (exacerbation rate for dupilumab 0·265 (0·157 to 0·445) versus exacerbation rate for placebo 0·897 (0·619 to 1·300)).				⊕⊕⊕◯ MODERATE	
EXACERBATION - annualised severe exacerbation event rate (dupilumab during 52 weeks)												
1	randomised trials	serious [c]	not serious [b]	not serious	not serious	none	NCT02414854 (Castro 2018) reported a risk reduction in event rates of 46% (32 to 57) in favour of 52 weeks of treatment (exacerbation rate for dupilumab 0.456 (0.389 to 0.534) versus exacerbation rate for placebo 0.970 (0.810 to 1.160))				⊕⊕⊕◯ MODERATE	
ASTHMA CONTROL (assessed with: ACQ-5 (dupilumab during 24 weeks); Scale from: 0 to 6)[d]												
2	randomised trials	serious [a,c]	not serious	not serious	not serious	none	790	479	-	least square MD **0.22 ACQ-5 units lower** (0.34 lower to 0.11 lower)	⊕⊕⊕◯ MODERATE	
ASTHMA CONTROL (assessed with: ACQ-5 (dupilumab during 52 weeks); Scale from: 0 to 6)[d]												
1	randomised trials	serious [c]	not serious [b]	not serious	not serious	none	633	321	-	least square MD **0.22 ACQ-5 units lower** (0.36 lower to 0.08 lower) [e]	⊕⊕⊕◯ MODERATE	
QUALITY OF LIFE (assessed with: AQLQ (dupilumab during 24 weeks); Scale from: 0 to 7)[f]												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	300 mg of dupilumab every 2 weeks	placebo	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	serious [a,c]	not serious	not serious	not serious	none	790	479	-	least square MD **0.23 AQLQ units higher** (0.03 higher to 0.43 higher)	⊕⊕⊕◯ MODERATE	
QUALITY OF LIFE (assessed with: AQLQ (dupilumab during 52 weeks); Scale from: 0 to 7)[f]												
1	randomised trials	serious [c]	not serious [b]	not serious	not serious	none	633	321	-	least square MD **0.26 AQLQ units higher** (0.12 higher to 0.4 higher) [e]	⊕⊕⊕◯ MODERATE	
SIDE EFFECTS (assessed with: any side effect (dupilumab during 24 weeks))												
1	randomised trials	serious [a]	not serious [b]	not serious	not serious	none	121/156 (77.6%)	118/158 (74.7%)	**RR 1.04** (0.92 to 1.18)	**3 more per 100** (from 6 fewer to 13 more)	⊕⊕⊕◯ MODERATE	
SIDE EFFECTS (assessed with: any side effect (dupilumab during 52 weeks))												
1	randomised trials	serious [c]	not serious [b]	not serious	not serious	none	515/632 (81.5%)	270/321 (84.1%)	**RR 0.97** (0.91 to 1.03)	**3 fewer per 100** (from 8 fewer to 3 more)	⊕⊕⊕◯ MODERATE	
SIDE EFFECTS (assessed with: any serious side effect (dupilumab during 24 weeks))												
1	randomised trials	serious [a]	not serious [b]	not serious	serious [g]	none	13/156 (8.3%)	9/158 (5.7%)	**RR 1.46** (0.64 to 3.32)	**3 more per 100** (from 2 fewer to 13 more)	⊕⊕◯◯ LOW	
SIDE EFFECTS (assessed with: any serious side effect (dupilumab during 52 weeks))												
1	randomised trials	serious [c]	not serious [b]	not serious	serious [h]	none	55/632 (8.7%)	27/321 (8.4%)	**RR 1.03** (0.67 to 1.61)	**0 fewer per 100** (from 3 fewer to 5 more)	⊕⊕◯◯ LOW	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	300 mg of dupilumab every 2 weeks	placebo	Relative (95% CI)	Absolute (95% CI)		
SIDE EFFECTS (assessed with: injection site reactions (dupilumab during 24 weeks))												
1	randomised trials	serious [a]	not serious [b]	not serious	serious [g]	none	41/156 (26.3%)	21/158 (13.3%)	**RR 1.98** (1.23 to 3.19)	**13 more per 100** (from 3 more to 29 more)	⊕⊕◯◯ LOW	
SIDE EFFECTS (assessed with: injection site reactions (dupilumab during 52 weeks))												
1	randomised trials	serious [c]	not serious [b]	not serious	serious [h]	none	116/632 (18.4%)	33/321 (10.3%)	**RR 1.79** (1.24 to 2.57)	**8 more per 100** (from 2 more to 16 more)	⊕⊕◯◯ LOW	

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. potential attrition bias in NCT01854047 (Wenzel 2016): trial report described an intention to treat analysis but results reported in tables does not fit with the intention to treat population
b. not applicable (findings from 1 trial)
c. potential attrition bias in NCT02414854 (Castro 2018): 75% participants completed the study. Reasons for discontinuation were not declared for 46% of patients that did not completed the 52 weeks intervention period.
d. minimal important difference for ACQ-5 is 0.5; lower values indicate better asthma control.
e. Castro 2018 reported effect estimates with standard errors. The effect estimated in the SoF table has been recalculated with the RevMan 5.3 statistical package
f. minimal important difference for AQLQ is 0.5; higher scores indicates better QoL.
g. low event rate, resulting in imprecise effect estimate
h. imprecision of results resulting from the results from Castro 2018 (planned treatment duration of 52 weeks)

Evidence Profile: 300 mg of dupilumab every 2 weeks compared to placebo for glucocorticoid dependent severe asthma

Bibliography: Rabe KF, Nair P, Brusselle G, Maspero JF, Castro M, Sher L, Zhu H, Hamilton JD, Swanson BN, Khan A, Chao J, Staudinger H, Pirozzi G, Antoni C, Amin N, Ruddy M, Akinlade B, Graham NMH, Stahl N, Yancopoulos GD, Teper A. Efficacy and Safety of Dupilumab in Glucocorticoid-Dependent Severe Asthma. N Engl J Med. 2018;378(26):2475-2485. doi: 10.1056/NEJMoa1804093.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	300 mg of dupilumab every 2 weeks	placebo	Relative (95% CI)	Absolute (95% CI)		
EXACERBATION - annualised severe exacerbation event rate (dupilumab during 24 weeks)												
1	randomised trials	not serious	not serious [a]	not serious	not serious	none	NCT02528214 (Rabe 2018) reported a risk reduction in event rates of 59·3% (37 to 73·7) favouring 24 weeks of treatment (exacerbation rate for dupilumab 0.649 (0.442 to 0.955) versus exacerbation rate for placebo 1.597 (1.248 to 2.043).				⊕⊕⊕⊕ HIGH	
ASTHMA CONTROL (assessed with: ACQ-5 (dupilumab during 24 weeks))[b]												
1	randomised trials	not serious	not serious [a]	not serious	serious [b]	none	NCT02528214 (Rabe 2018) reported a least square MD of −0.47 (−0.76 to −0.18) favouring 24 weeeks of treatment with dupilumab				⊕⊕⊕◯ MODERATE	
LUNG FUNCTION (change in FEV1 from baseline to end of treatment) (assessed with: liters)												
1	randomised trials	not serious	not serious [a]	not serious	serious [c]	none	NCT02528214 (Rabe 2018) reported a least square MD of 0.22 (0.09 to 0.34) L favouring 24 weeeks of treatment with dupilumab (dupilumab 0.22 (0.05) versus placebo 0.01 (0.05)).				⊕⊕⊕◯ MODERATE	
SYSTEMIC STEROIDS USE (patients with ≥50% reduction in oral glucocorticoid dose at 24 w)												
1	randomised trials	not serious	not serious [a]	not serious	not serious	none	82/103 (79.6%)	57/107 (53.3%)	**RR 1.49** (1.22 to 1.83)	**26 more per 100** (from 12 more to 44 more)	⊕⊕⊕⊕ HIGH	
SYSTEMIC STEROIDS USE (patients with oral glucocorticoid reduced to <5 mg/day at 24 w)												
1	randomised trials	not serious	not serious [a]	not serious	not serious	none	74/103 (71.8%)	40/107 (37.4%)	**RR 1.92** (1.46 to 2.53)	**344 more per 1.000** (from 172 more to 572 more)	⊕⊕⊕⊕ HIGH	
SYSTEMIC STEROIDS USE (patients with maximum possible reduction of oral glucocorticoid dose at 24 w)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	300 mg of dupilumab every 2 weeks	placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious [a]	not serious	not serious	none	54/103 (52.4%)	32/107 (29.9%)	**RR 1.75** (1.24 to 2.47)	**224 more per 1.000** (from 72 more to 440 more)	⊕⊕⊕⊕ HIGH	

SYSTEMIC STEROIDS USE (patients no longer requiring oral glucocorticoid at 24 w)

1	randomised trials	not serious	not serious [a]	not serious	not serious	none	54/103 (52.4%)	31/107 (29.0%)	**RR 1.81** (1.28 to 2.57)	**235 more per 1.000** (from 81 more to 455 more)	⊕⊕⊕⊕ HIGH	

SIDE EFFECTS (assessed with: any side effect (dupilumab during 24 weeks))

1	randomised trials	not serious	not serious [a]	not serious	serious [d]	none	64/103 (62.1%)	69/107 (64.5%)	**RR 0.96** (0.78 to 1.18)	**3 fewer per 100** (from 14 fewer to 12 more)	⊕⊕⊕◯ MODERATE	

SIDE EFFECTS (assessed with: any serious side effect (dupilumab during 24 weeks))

1	randomised trials	not serious	not serious [a]	not serious	serious [d]	none	9/103 (8.7%)	6/107 (5.6%)	**RR 1.56** (0.58 to 4.22)	**3 more per 100** (from 2 fewer to 18 more)	⊕⊕⊕◯ MODERATE	

SIDE EFFECTS (assessed with: injection site reactions (dupilumab during 24 weeks))

1	randomised trials	not serious	not serious [a]	not serious	serious [d]	none	9/103 (8.7%)	4/107 (3.7%)	**RR 2.34** (0.74 to 7.35)	**5 more per 100** (from 1 fewer to 24 more)	⊕⊕⊕◯ MODERATE	

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. not applicable (findings from 1 trial)
b. minimal important difference for ACQ-5 is 0.5; lower values indicate better asthma control.
c. minimal important difference for FEV1 is 0.23.
d. low event rate, resulting in imprecise effect estimate

Evidence Profile: 200 mg of dupilumab every 2 weeks compared to placebo for patients with severe asthma according to blood eosinophils

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	200 mg of dupilumab every 2 weeks	placebo	Relative (95% CI)	Absolute (95% CI)		
EXACERBATION - annualised severe exacerbation event rate at week 24 (according to blood eosinophil 300 cells/mm3 or more)												
1 [1]	randomised trials	not serious	not serious [a]	not serious	not serious	none	0/65	0/68	**Rate ratio 0.29** (0.11 to 0.76)	**74 less severe exacerbations per 100 patients per year** (from 44 to 122)	⊕⊕⊕⊕ HIGH	
EXACERBATION - annualised severe exacerbation event rate at week 24 (according to blood eosinophil <300 cells/mm3)												
1 [1]	randomised trials	not serious	not serious [a]	not serious	not serious	none	0/85	0/90	**Rate ratio 0.32** (0.14 to 0.74)	**53 less severe exacerbations per 100 patients per year** (from 37 to 71)	⊕⊕⊕⊕ HIGH	
LUNG FUNCTION - change in FEV1 from baseline at week 24 (according to blood eosinophil 300 cells/mm3 or more) (assessed with: Liters)												
1 [1]	randomised trials	serious [b]	not serious [a]	not serious	serious [c]	none	59	52	-	least square **0.16 Liters more** (0.02 more to 0.31 more)	⊕⊕◯◯ LOW	
LUNG FUNCTION - change in FEV1 from baseline at week 24 (according to blood eosinophil <300 cells/mm3) (assessed with: Liters)												
1 [1]	randomised trials	serious [b]	not serious [a]	not serious	serious [c]	none	76	73	-	least square **0.14 Liters more** (0.03 more to 0.25 more)	⊕⊕◯◯ LOW	
LUNG FUNCTION - change in FEV1 from baseline at week 24 (according to blood eosinophil 300 cells/mm3 or more) (assessed with: % of change; Scale from: 0 to 100)												
1 [1]	randomised trials	serious [b]	not serious [a]	not serious	serious [d]	none	59	52	-	least square **10.07 percentage points more** (1.23 more to 18.9 more)	⊕⊕◯◯ LOW	
LUNG FUNCTION - change in FEV1 from baseline at week 24 (according to blood eosinophil <300 cells/mm3) (assessed with: % of change; Scale from: 0 to 100)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	200 mg of dupilumab every 2 weeks	placebo	Relative (95% CI)	Absolute (95% CI)		
1 [1]	randomised trials	serious [b]	not serious [a]	not serious	serious [d]	none	76	73	-	least square **8.75 percentage points more** (2.7 more to 14.81 more)	⊕⊕◯◯ LOW	
ASTHMA CONTROL - at week 24 according to blood eosinophil 300 cells/mm3 or more (assessed with: ACQ-5; Scale from: 0 to 6)[e]												
1 [1]	randomised trials	serious [b]	not serious [a]	not serious	serious [c]	none	59	52	-	least square MD **0.42 ACQ-5 units lower** (0.76 lower to 0.07 lower)	⊕⊕◯◯ LOW	
ASTHMA CONTROL - at week 24 according to blood eosinophil <300 cells/mm3 (assessed with: ACQ-5; Scale from: 0 to 6)[e]												
1 [1]	randomised trials	serious [b]	not serious [a]	not serious	serious [c]	none	75	75	-	least square MD **0.33 ACQ-5 units lower** (0.61 lower to 0.05 lower)	⊕⊕◯◯ LOW	
QUALITY OF LIFE - at week 24 according to blood eosinophil 300 cells/mm3 or more (assessed with: AQLQ ; Scale from: 0 to 7)[f]												
1 [1]	randomised trials	serious [b]	not serious [a]	not serious	serious [c]	none	58	53	-	least square MD **0.67 AQLQ units higher** (0.31 higher to 1.03 higher)	⊕⊕◯◯ LOW	
QUALITY OF LIFE - at week 24 according to blood eosinophil <300 cells/mm3 (assessed with: AQLQ; Scale from: 0 to 7)[f]												
1 [1]	randomised trials	serious [b]	not serious [a]	not serious	not serious	none	74	74	-	least square MD **0.05 AQLQ units higher** (0.26 lower to 0.36 higher)	⊕⊕⊕◯ MODERATE	

CI: Confidence interval

Explanations

a. not applicable (findings from 1 trial)

b. Relevant and differential attrition bias in NCT01854047 (Wenzel 2016) for placebo and dupilumab groups (more than 20% and around 10% respectively)

c. the lower CI boundary crosses the threshold for minimal important difference

d. Minimal important differences not known for FEV1 % of change, however the 95CI is wide and does not exclude important benefit or no effect.

e. minimal important difference for ACQ-5 is 0.5; lower values indicate better asthma control.
f. minimal important difference for AQLQ is 0.5; higher scores indicates better QoL.

References

1. Wenzel S, Castro M,Corren J,Maspero J,Wang L,Zhang B,Pirozzi G,Sutherland ER,Evans RR,Joish VN,Eckert L,Graham NM,Stahl N, Yancopoulos GD,Louis-Tisserand M,Teper A.. Dupilumab effi cacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting β2 agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial. Lancet; 2016.

Evidence to Decision Framework:DUPILUMAB

Should an anti-interleukin 4/13 strategy be used for adults and children with severe asthma?

POPULATION:	Adults and children with severe asthma	**BACKGROUND:**
INTERVENTION:	Anti-interleukin 4/13 strategy (dupilumab, a monoclonal antibody directed against the interleukin 4 receptor subunit alpha)	Approximately half of patients with asthma exhibit elevated markers of type 2 inflammation. Two of the cytokines that orchestrate this type of inflammation are interleukins (IL) 4 and 13, each of which independently elicits pathobiologic changes in airway structural and immune cells characteristic of asthma. IL4 is required for the skewing of T helper cells into Th2 cells, and for the switching of B cell antibody production into the IgE isotype crucial for allergic inflammation. IL13 is a prime inducer of airway hyperresponsiveness and is implicated in airway remodeling. Both cytokines engage and signal through the interleukin 4 receptor subunit alpha. A monoclonal antibody that targets the interleukin 4 receptor subunit alpha, dupilumab, has been found to be efficacious in randomized controlled trials to improve asthma-related outcomes. This systematic review and meta-analysis synthesizes the data from three randomized controlled trials that have investigated the anti-IL4/13 strategy and provides treatment recommendations based on the results.
COMPARISON:	No anti-interleukin 4/13	
MAIN OUTCOMES:	Rate of exacerbations Time to first asthma exacerbation Asthma exacerbations requiring ER visits or hospitalization Lung function Asthma control Maintenance corticosteroid dose reduction Adverse events Serious adverse events Quality of life	

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○Don't know	Asthma exacerbations are a critically important outcome for the patients with asthma who experience these and the clinicians who care for them. Relative to participants assigned to placebo, those assigned to dupilumab experienced substantial (46-70.5%) reduction in their rates of asthma exacerbations (PMID: 29782224, PMID: 29782217, PMID: 27130691) (insert evidence tables for the two doses and time intervals). One RCT evaluated the effects of dupilumab therapy in oral corticosteroid (OCS) dependent asthma (Rabe 2018. PMID: 29782224). Dupilumab therapy was associated with greater number of participants that experienced $\geq$ 50% reduction in OCS dose (RR 1.49; 95% Ci 1.22-1.83), were able to reduce OCS dose to < 5mg/d (RR 1.92; 95% CI 1.46-2.53) and were able to discontinue maintenance OCS (RR 1.81; 95% CI 1.28-2.57). Asthma symptom scores are another critically important outcome in asthma studies. Although the evidence favors dupilumab relative to placebo on these outcomes, their relative change was not as large compared to the improvement observed with asthma exacerbations. Relative to participants assigned to placebo, those assigned to dupilumab experienced a 0.22-0.47 point decrease (i.e. improvement) in Asthma Control Questionnaire (ACQ) (insert evidence table). Although statistically significant, these decreases in ACQ-5 scores did not surpass the 0.5-point MCID for the ACQ symptom score for trials in asthma. Similarly, although the improvements in lung function (FEV1) were statistically significant (see evidence tables), they were small and did not cross the MCID threshold of 0.23 L. Efficacy is similar between doses. The effect size for all above outcomes was larger in subgroup of patients with higher blood eosinophil count. Meta-analytical results on other outcomes appear in the online supplement.	Although a defined threshold for clinically meaningful reductions in asthma exacerbations has not been universally agreed upon, the effect sizes in reductions in asthma exacerbations for this drug would be considered clinically substantial by most practitioners. The decision to consider changes in lung function [forced expiratory volume in the first second (FEV1)] as 'important' outcomes as opposed to 'critical' outcomes is due to their place relative to other critical outcomes. We understand that most clinicians would prescribe dupilumab due to its efficacy in reducing asthma exacerbations despite only modest improvements in lung function. Results from our meta-analysis on the modest effect on lung function relative to the effect on asthma exacerbations led us to downgrade the importance of lung function to an important outcome, as suggested by the methodological approach endorsed by Guyatt et al (PMID: 21194891) Taken together, the reduction in asthma exacerbations is substantial enough for this committee to judge the desirable effects of an anti-IL4/13 strategy as large, regardless of relatively smaller effects on symptom scores and lung function. Dupilumab is currently FDA approved in patients $\geq$ 12 years of age with moderate to severe eosinophilic asthma or those with systemic corticosteroid dependent asthma. Dupilumab is available in two doses for

			indication of asthma: 200 mg every 2 weeks after a loading dose of 400 mg; 300 mg every 2 weeks after a loading dose of 600 mg. This panel agrees with FDA recommendation to consider the higher dose for patients with OCS dependent asthma or comorbid atopic dermatitis. FDA notes that "the adolescent subgroup demonstrated a statistically significant improvement in lung function for both dose groups; however, the exacerbation benefit was not clearly demonstrated for either dose group. This review recommends approval in this age group, as there are no age-related differences in the pharmacokinetic and pharmacodynamic parameters, and no safety concerns for dupilumab in adolescent patients."
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	In the RCTs analysed, the relative risk of a study participant developing an adverse event was 0.96-1.08 for those participants assigned to dupilumab compared to placebo. Similarly, the relative risk of participant developing a serious adverse event when assigned to dupilumab vs. placebo was 0.93-1.56. (insert evidence tables). Relative risk for injection site reactions varied from 1.47 (95% CI 0.88-2.47; 200 mg dose at 24 weeks) to 2.34 (95% CI 0.74-7.35; 300 mg dose at 24 weeks)	Dupilumab has been well tolerated, receiving its first FDA approval for atopic dermatitis in 2017 followed by its approval for asthma in 2018. Treatment related eosinophilia that met criteria for adverse event was observed in 4.1% of participants assigned to dupilumab vs. 0.6% in those assigned to placebo (PMID: 29782217). Associated symptoms of eosinophilia were noted in 0.2% of the total trial population in this study. Similarly, in another study of patients with corticosteroid-dependent asthma (PMID: 29782224), treatment related eosinophilia AE was observed in 13% of participants as compared to 1% of participants assigned to placebo. Long term follow-up for this and other side effects is unavailable. Monitoring for eosinophilia is not mandated in the package insert. Injection site reactions were the most common side effects and were dose-

			related. The ocular side effects seen in studies of dupilumab in atopic dermatitis were not observed in asthma trials.
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ○ Very low ○ Low ● Moderate ○ High ○ No included studies	Overall population (patients with moderate and severe persistent asthma): low quality of evidence; Population that meets criteria for the diagnosis of severe asthma defined by the ERS/ATS Guidelines: low quality of evidence	Our certainty assessment relies on study design (randomized controlled trials), risk of bias (not serious), inconsistency (not serious), indirectness (not serious), and imprecision (not serious). Further the certainty is based on the quality of evidence that is lowest among critical outcomes.
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability ○ No known undesirable outcomes	No evidence identified	There is no important uncertainty about how patients and the clinicians who care for them assess asthma exacerbations. On the other hand, asthma exacerbations are not the only critical outcome for patients and clinicians, who also consider the effect of interventions on other outcomes, such as changes in lung function, change in maintenance dose of systemic corticosteroids, asthma symptoms, and quality of life. Although the effect size of anti-IL4/13 strategy drug is not uniform across these other outcomes, these drugs tended to improve to varying degrees all asthma related outcomes. Further, patients and clinicians rarely decide to prescribe these drugs based on only one of these outcomes in isolation. Further, many pharmacy formularies for

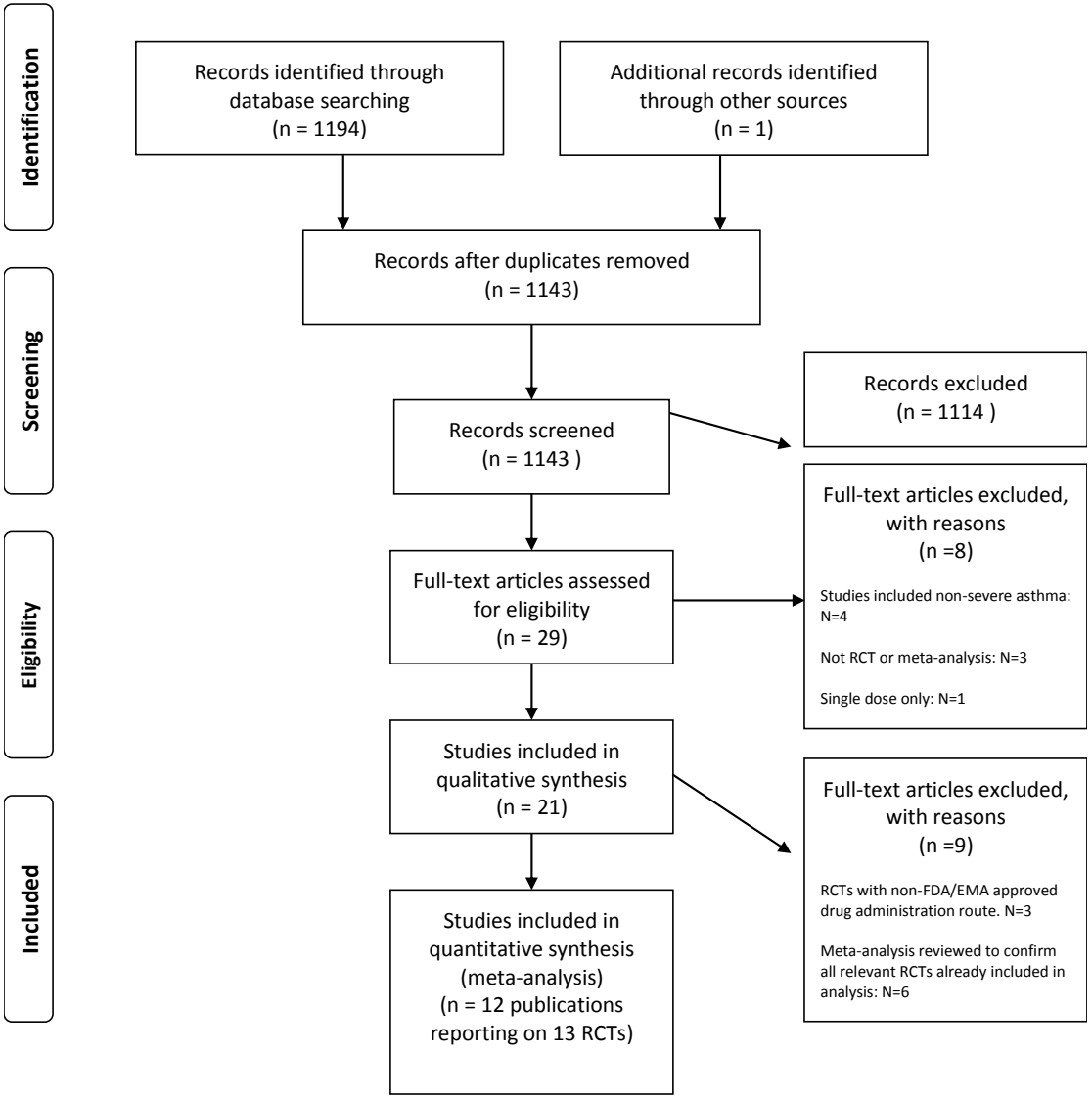
			physician groups and hospitals restrict these drugs to patients with severe asthma and a recent history of asthma exacerbations. The decision whether or not to prescribe these drugs is likely to be important in this population.
BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ Don't know	Dupilumab therapy was associated with large desirable and small undesirable effects.	Dupilumab was well tolerated in the clinical trials. Frequency of both serious and non-serious side effects were similar in placebo and intervention groups. Thus, considering the substantial benefit in terms of reducing asthma exacerbations, the balance favors using an anti-IL4/13 strategy.
AYBCOST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ● Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	The December 2018 report by the Institute for Clinical and Economic Review (ICER) states that dupilumab costs >$400,000 per quality-adjusted life years (QALY) gained when compared to standard of care (ICER 2018). These figures far exceed the accepted threshold for a cost-effective intervention of $150,000 per QALY gained.	Therefore, the alternative is favored over an anti-IL4/13 strategy from a cost-effectiveness standpoint.
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ○ Low ○ Moderate ● High ○ No included studies	The manufacturers' listed annual net price for dupilumab is $36,000 (ICER 2018). The certainty of these costs is therefore high.	
EQUITY	**What would be the impact on health equity?**	No evidence identified.	In the US, racial and ethnic minorities, and individuals of lower socioeconomic

	○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know		status have been documented to have less access to specialty clinics and are less likely to use controller therapy for asthma. Since dupilumab is mainly prescribed by specialists it is likely that racial and ethnic minorities will be less likely to be prescribed one of these drugs. Other groups may thus experience greater reductions in asthma exacerbations due to access to these drugs, which will thus reduce health equity. Similarly, patients with severe asthma who live in regions with fewer specialists will be less likely to receive these drugs, thus reducing equity between areas with high and low access to specialty care. On the other hand, the manufacturers of these drugs have programs in place to reduce patients' out of pocket costs for these drugs, which may partly mitigate the decrease in equity posed by differences in access by socioeconomic status and race/ethnicity.
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	No evidence identified.	Most patients with severe asthma welcome the possibility of relief from asthma through dupilumab, as long as the potential benefit is not offset by adverse effects, costs or other inconveniences (travel or prolonged waiting times in clinic, etc.). Health insurance companies and clinic administrations find anti-IL4/13 strategy drugs less acceptable due to their high cost.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ○ Probably yes ○ Yes	No evidence identified.	The feasibility to implement is dependent on many variables including access to asthma specialists, clinical resources to train patients to self-administer this drug, clinical set up that allows close follow-up of patients on

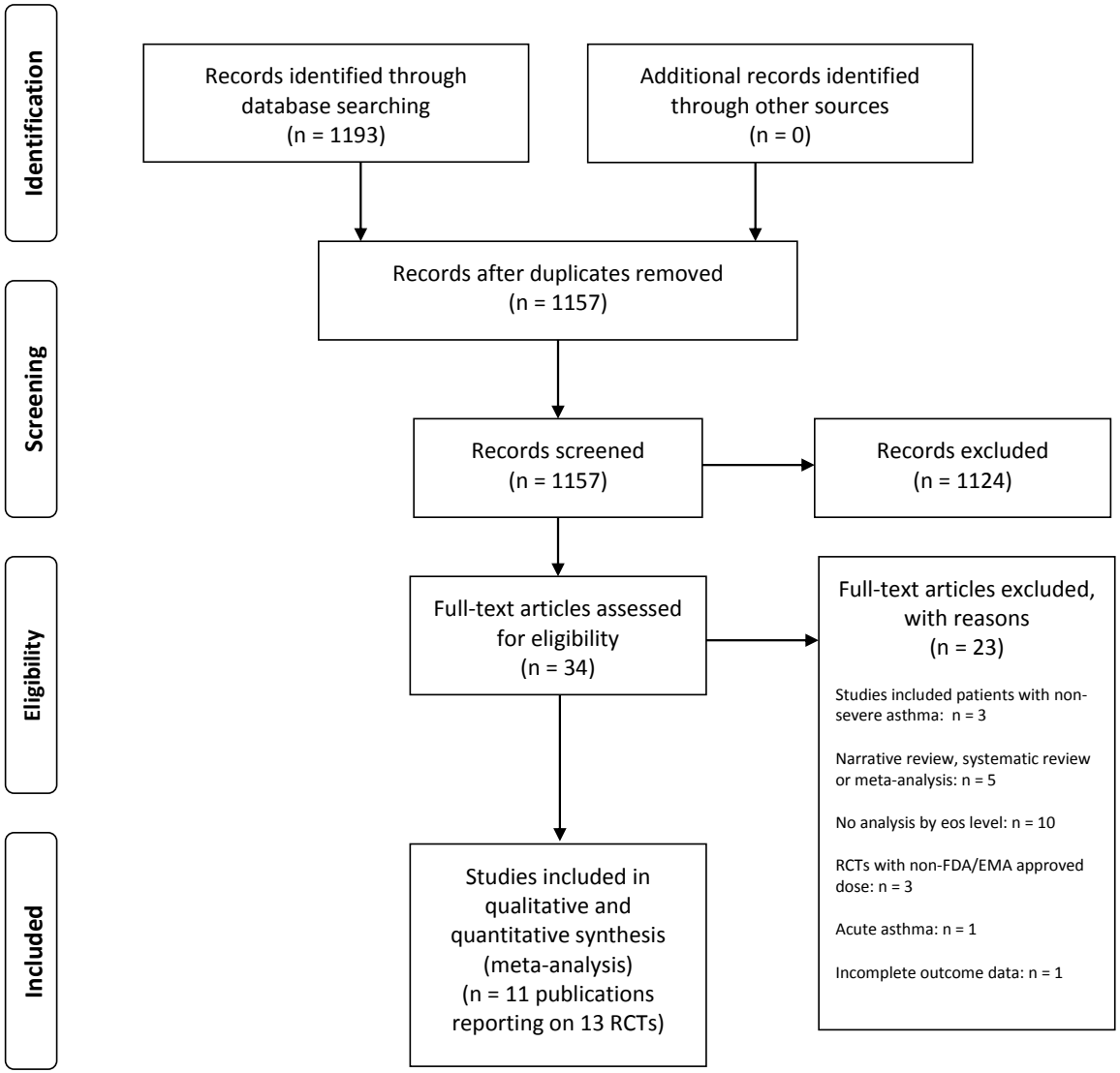
	● Varies ○ Don't know		therapy, as well as a laboratory that can measure blood eosinophils in these patients. Patients without access to these resources are unlikely to receive this therapy.

PRISMA FLOW CHARTS

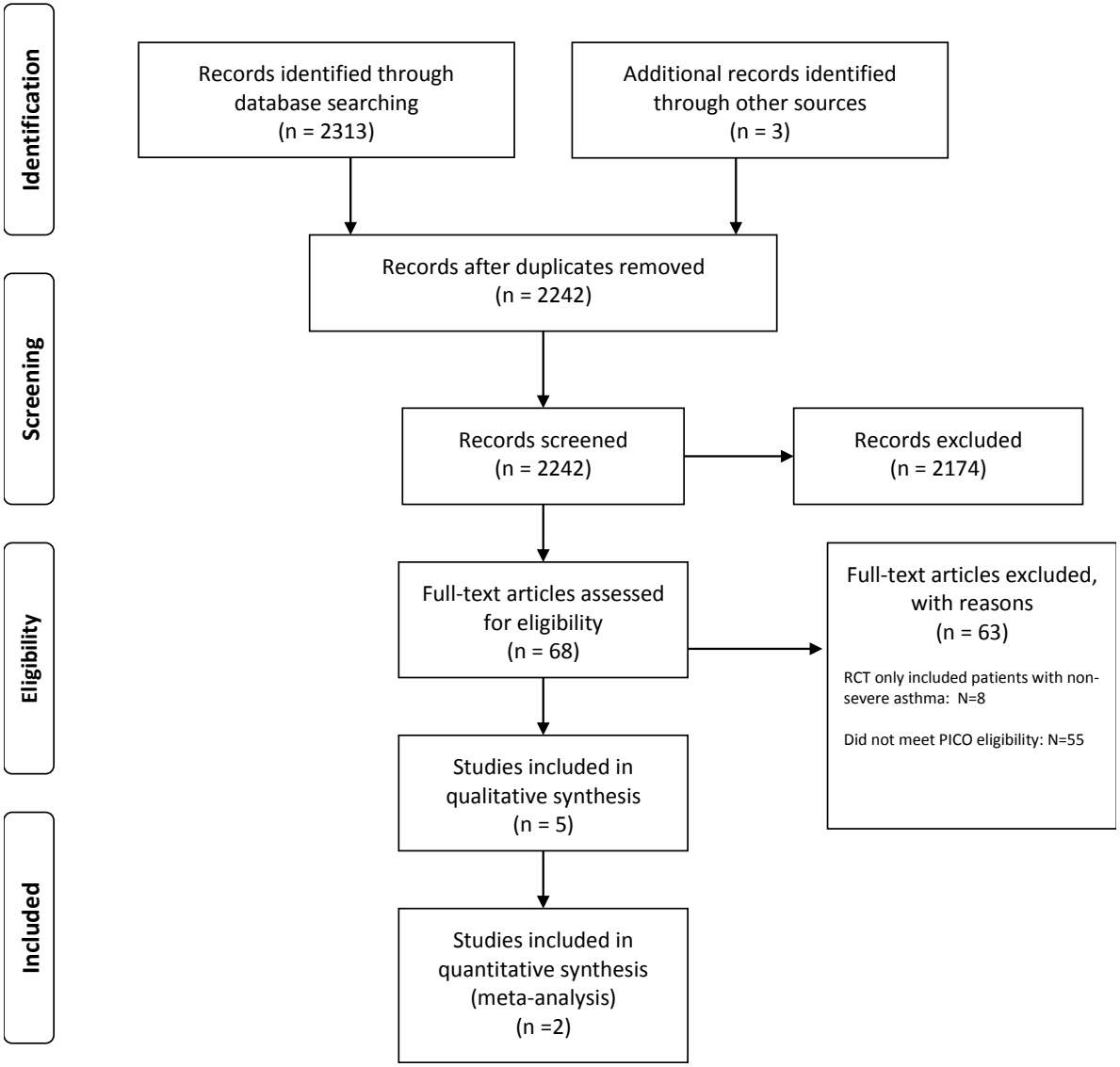
Should a monoclonal anti-IL5 antibody be used in adults and children with severe asthma?



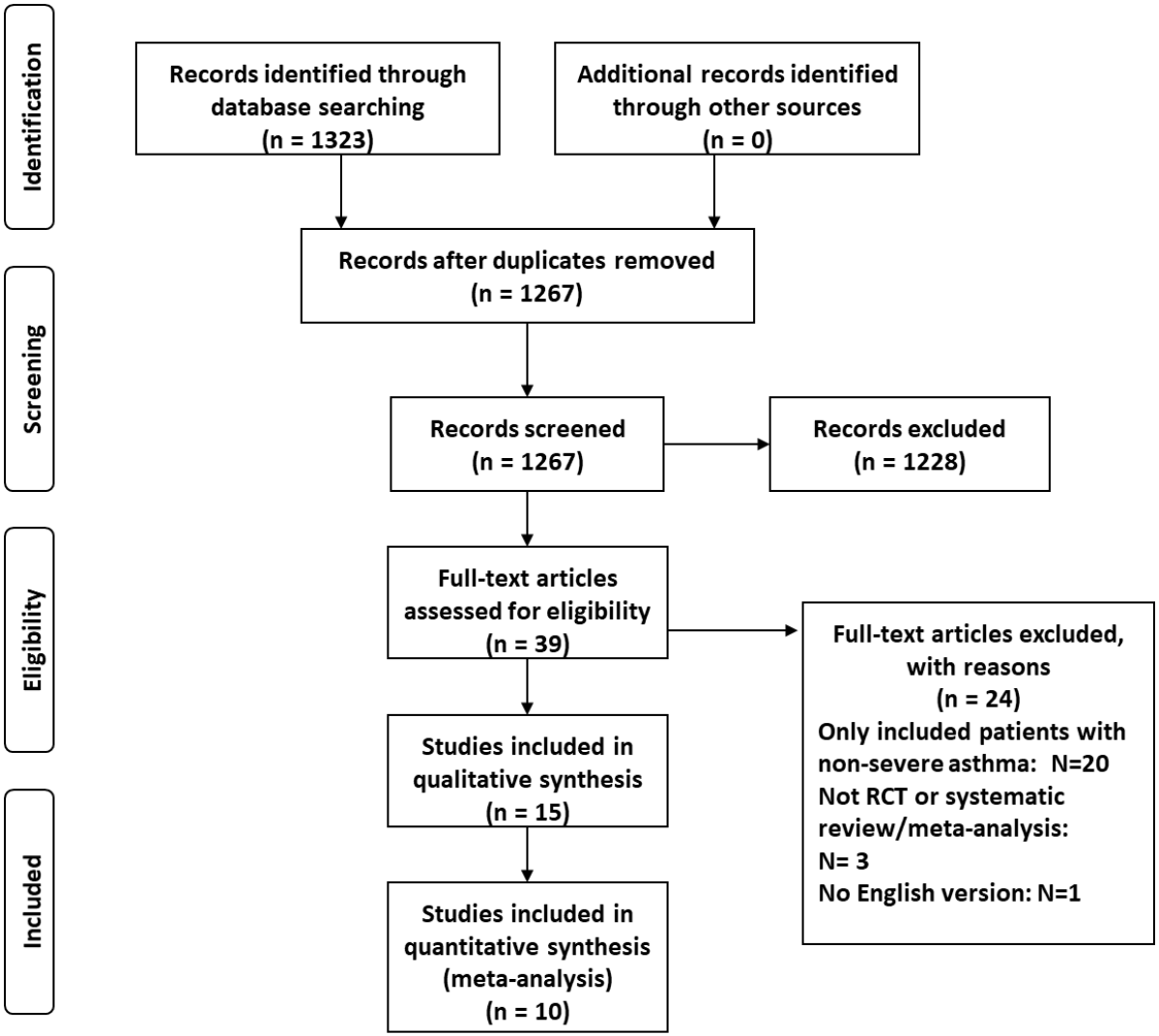
Should a measurement of a specific biomarker be used to guide initiation of treatment with a monoclonal anti-IL5 or IL5Rα antibody in adults and children with severe asthma? (biomarkers being exhaled NO, peripheral or sputum eosinophils, and serum periostin)



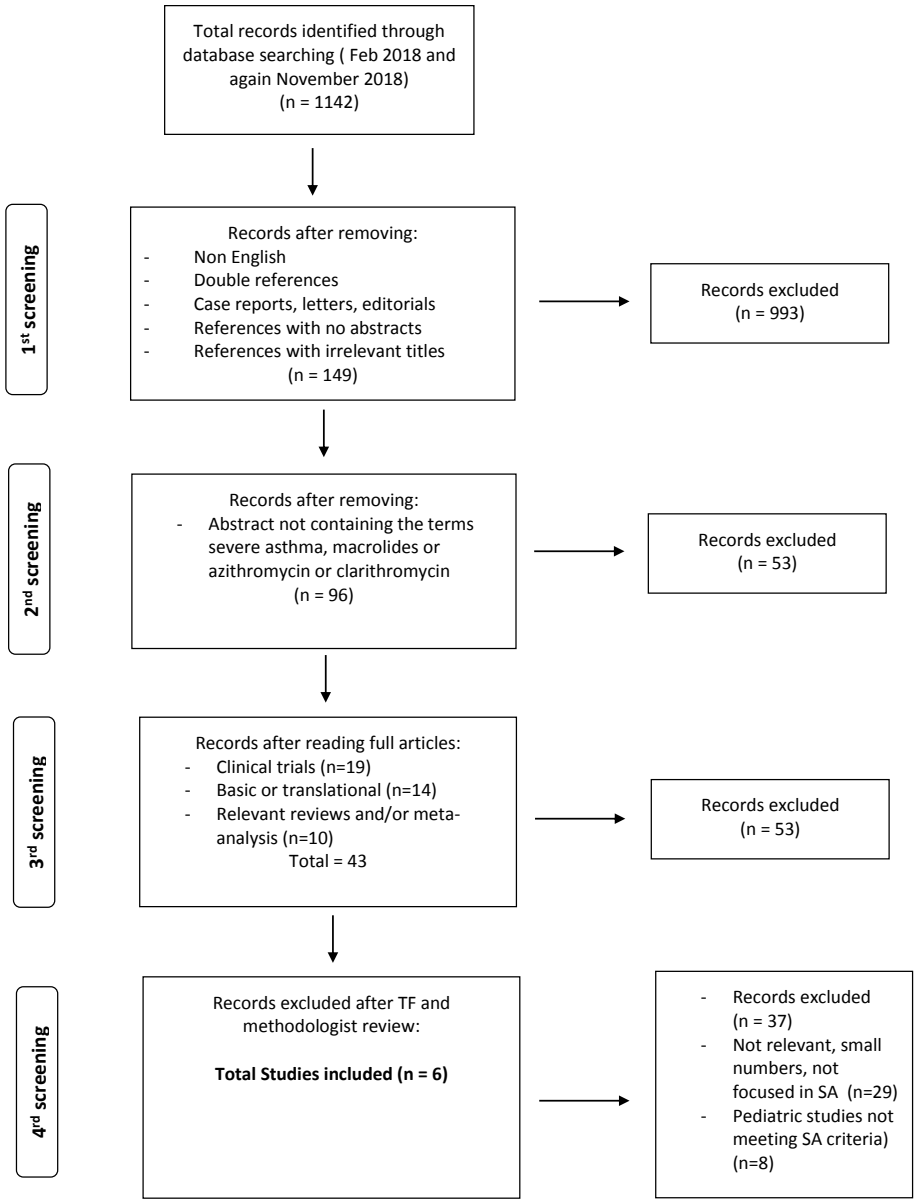
Should a measurement of a specific biomarker be used, in addition to total IgE level, to guide initiation of treatment with a monoclonal anti-IgE antibody in adults and children with severe asthma? (biomarkers being exhaled NO, peripheral or sputum eosinophils, and serum periostin)



Should a long-acting inhaled muscarinic antagonist (LAMA) be used in adults and children with severe asthma?



Should a macrolide (i.e., azithromycin, clarithromycin) be used in adults and children with severe asthma?



Should an anti-interleukin 4/13 strategy be used for adults and children with severe asthma?