



Management of severe asthma: a European Respiratory Society/American Thoracic Society guideline

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The ERS/ATS Task Force makes recommendations on the use of novel therapies for severe asthma, specifically biologicals for type 2 high asthma, and antimuscarinic agents and macrolides, as well as on biomarkers for predicting treatment response <http://bit.ly/2kZLRaD>

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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 European Respiratory Society/American Thoracic Society Task Force's questions. The evidence was appraised using the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach and the results were summarised in evidence profiles. The evidence syntheses were discussed and recommendations formulated by a multidisciplinary Task Force of asthma experts, who made specific recommendations on six 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-interleukin (IL)-5 and anti-IL-5 receptor α for severe uncontrolled adult eosinophilic asthma phenotypes; 2) suggest using a blood eosinophil cut-point $\geq 150 \mu\text{L}^{-1}$ to guide anti-IL-5 initiation in adult patients with severe asthma; 3) suggest considering specific eosinophil ($\geq 260 \mu\text{L}^{-1}$) and exhaled nitric oxide fraction (≥ 19.5 ppb) cut-offs to identify adolescents or adults with the greatest likelihood of response to anti-IgE therapy; 4) suggest using inhaled tiotropium for adolescents and adults with severe uncontrolled asthma despite Global Initiative for Asthma (GINA) step 4–5 or National Asthma Education and Prevention Program (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; and 6) suggest using anti-IL-4/13 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.

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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 [1]:

When a 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 which 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 fraction (F_{ENO}) 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 biological treatments approved for the management of severe eosinophilic asthma. Six specific and important questions were formulated using the PICO (Patient population, Intervention, Comparison and Outcome) format. The GRADE (Grading of Recommendations, Assessment, Development and Evaluation) 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.

During the deliberations of the Task Force, it became clear that the interleukin-4 receptor α (IL-4R α) blocker dupilumab, which modulates the effects of IL-4 and IL-13, would receive approval by the regulatory authorities, so the sixth PICO was instituted, having originally not been considered. The current 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 synthesise, formulate and grade the evidence is available in previous ERS/ATS guidelines and in the supplementary material [3, 4].

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TABLE 1 European Respiratory Society (ERS)/American Thoracic Society (ATS) Severe Asthma Task Force questions

- 1 Should a monoclonal anti-IL-5 antibody be used in adults and children[#] with severe asthma?
- 2 Should a measurement of a specific biomarker be used to guide initiation of treatment with a monoclonal anti-IL-5 or IL-5R α antibody in adults and children with severe asthma? (Chosen biomarkers being F_{ENO} , 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 F_{ENO} , peripheral or sputum eosinophils and serum periostin)
- 4 Should a long-acting inhaled muscarinic antagonist 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-IL-4R α be used in adults and children with severe asthma?

IL: interleukin; R: receptor; F_{ENO} : exhaled nitric oxide fraction. [#]: for the purposes of this guideline, age >5 years.

Group composition

The ERS and ATS selected the Task Force co-chairs (Fernando Holguin and Andy Bush), who led the project and selected the other panellists, who included 23 clinicians and researchers with experience in severe asthma and two severe asthma patient representatives (Betty Frankemölle and Dominique Hamerlijnc). Two methodologists (David Rigau and Rebecca L. Morgan), led by the ERS senior methodologist (Thomy Tonia), supervised and ensured that all the methodological requirements were met. Systematic reviews and application of the GRADE approach were performed by members of the Task Force (Diogenes S. Ferreira and Sarah Diver) and externally commissioned (Iberoamerican Cochrane Centre, Barcelona, Spain). The methodologists 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 panellists discussed the evidence and formulated the recommendations. Evidence profiles and Evidence to Decision tables (supplementary material) developed with the GRADEpro Guideline Development Tool (grade.pro.org) were used to facilitate the discussion, 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 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 conflict of interest.

Thresholds for minimum clinically important differences (MCIDs) 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 points, Asthma Control Questionnaire (ACQ-5, ACQ-6 and ACQ-7) score change of 0.5 points, Asthma Quality of Life Questionnaire (AQLQ) score change of 0.5 points and forced expiratory volume in 1 s (FEV_1) change of 0.23 L (10.38% change from baseline) [5–7].

Literature searches

The librarians (Shandra Knight and Liz Kellermeyer) conducted the literature search strategies in MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE, Embase and Cochrane Central Register of Controlled Trials, beginning in 2008 and ending with a final update on September 27, 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 populations receiving the interventions of interest. We excluded phase 1 (pharmacokinetic or pharmacodynamic studies), real-life nonrandomised extension studies and research reported in abstract form only (*e.g.* 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, experts were contacted 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 supplementary material. Judgements on the quality of evidence were reviewed by the Task Force members and validated by the ERS methodologists (Thomy Tonia, David Rigau and Rebecca L. Morgan).

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 e-mail, 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.

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 a 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 a 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 panellist (Kian Fan Chung) developed the initial manuscript draft. The ERS methodologists and PICO leaders prepared the Evidence to Decision 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 supplementary material.

Results

Question 1: Should a monoclonal anti-IL-5 antibody be used in adults and children with severe asthma?

IL-5 is a principal cytokine driving eosinophilic inflammation in asthma. Monoclonal antibodies that target IL-5 (mepolizumab, reslizumab) or its receptor IL-5R α (benralizumab) have been found to be efficacious in randomised controlled trials in improving asthma-related outcomes and are currently approved by the US Federal Drug Administration (FDA)/European Medicines Agency (EMA). We identified 12 randomised controlled trials that met inclusion criteria [8–19]. We included data only for participants on FDA/EMA licensed doses or the 20 mg subcutaneous dose from phase 2 benralizumab trials. The evidence from meta-analyses of these trials is summarised in the following section. 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 randomised placebo-controlled trials in patients with severe eosinophilic asthma (blood eosinophil count $\geq 300 \mu\text{L}^{-1}$ in the 12 months prior to screening or $\geq 150 \mu\text{L}^{-1}$ during screening/oral corticosteroid (OCS) optimisation period) considered by this Task Force to represent a population of severe asthma subjects as defined by the ERS/ATS guidelines on severe asthma. Two studies required patients to have had at least two exacerbations in the previous year despite regular use of high-dose inhaled corticosteroid (ICS) plus another controller [9, 10], whereas the other study 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⁻¹·year⁻¹) and 64% reduction in exacerbations requiring an emergency department visit or hospitalisation (rate ratio 0.36, 95% CI 0.20–0.66; absolute risk 0.05 *versus* 0.15 events·patient⁻¹·year⁻¹). Compared with placebo, those assigned to

mepolizumab experienced an absolute 0.43-point decrease (*i.e.* improvement) in ACQ-5 (95% CI -0.56 – -0.31 points) and an absolute 7.14-point decrease (*i.e.* improvement) in SGRQ (95% CI -9.07 – -5.21 points). Mepolizumab, relative to placebo, resulted in a 50% median (95% CI 20–75%) reduction in the dose of maintenance OCS in one study of 135 patients [8]. The effect of mepolizumab on FEV₁ was less than the MCID threshold.

Reslizumab

Four publications that included five randomised controlled trials met the inclusion criteria [11–14]. CASTRO *et al.* [13] reported on two duplicate trials. Three of the five randomised controlled trials included adolescents in addition to adult participants [11, 13]. All studies except one [12] included patients with mixed severity (moderate and severe) asthma. Three randomised controlled trials used inclusion criteria of blood eosinophils $\geq 400 \mu\text{L}^{-1}$ [11, 13, 14] and one randomised controlled trial used sputum eosinophils $\geq 3\%$ [12]. One randomised controlled trial included participants unselected for blood eosinophil count, but subsequently performed a subgroup analysis using a blood eosinophil cut-off of $400 \mu\text{L}^{-1}$ [14]. Overall, reslizumab therapy was associated with a 54% reduction in any exacerbation (rate ratio 0.46, 95% CI 0.37–0.58; absolute risk 0.84 *versus* 1.81 events-patient⁻¹.year⁻¹) relative to placebo and 33% reduction in exacerbations requiring emergency department visits or hospitalisations (rate ratio 0.67, 95% CI 0.39–1.17; absolute risk 0.077 *versus* 0.12 events-patient⁻¹.year⁻¹). Reslizumab therapy also reduced the risk of patients having at least one exacerbation (29.2% *versus* 46.7%; risk ratio 0.63, 95% CI 0.53–0.76). In study participants meeting ERS/ATS criteria for diagnosis of severe asthma, reslizumab therapy was associated with a 60% reduction in the risk of having one or more exacerbations (7.5% *versus* 18.9%; risk ratio 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 points) and an absolute 0.28-point increase (*i.e.* improvement) in AQLQ (95% CI 0.17–0.39 points). The effect of reslizumab on FEV₁ did not cross the MCID threshold.

Benralizumab

Five randomised controlled trials 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 randomised controlled trials 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; absolute risk 0.64 *versus* 1.19 events-patient⁻¹.year⁻¹) and a 38% reduction in the number of patients with one or more exacerbations (35.9% *versus* 51.1%; risk ratio 0.62, 95% CI 0.36–1.06) relative to placebo. In study participants meeting ERS/ATS criteria for diagnosis of severe asthma, benralizumab therapy was associated with 55% reduction in exacerbations (number of patients with one or more exacerbations 23.3% *versus* 52%; risk ratio 0.45, 95% CI 0.28–0.72). Those requiring emergency department visits or hospitalisations were also reduced (rate ratio 0.45, 95% CI 0.14–1.47; absolute risk 0.043 *versus* 0.18 events-patient⁻¹.year⁻¹) and with a greater magnitude for patients meeting ERS/ATS criteria for diagnosis of severe asthma (rate ratio 0.07, 95% CI 0.01–0.63; absolute risk 0.02 *versus* 0.32 events-patient⁻¹.year⁻¹)

Relative to participants on placebo, those assigned to benralizumab experienced an absolute 0.29-point decrease (*i.e.* improvement) in ACQ-6 (95% CI -0.4 – -0.17 points) and an absolute 0.32-point increase (*i.e.* improvement) in AQLQ (95% CI 0.19–0.45 points). The effect of benralizumab on FEV₁ was below the MCID. The median OCS dose reduction from baseline (range) at the final visit (week 28) was 25.0% (-150 – 100%) in the placebo group (n=75) and 75.0% (-50 – 100%) in the benralizumab group (n=73) [18].

Adverse effects

Compared with 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-IL-5 strategy drugs (supplementary material). 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 three mepolizumab trials, but only from two out of five reslizumab trials and one out of five 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%; risk ratio 1.35, 95% CI 1.01–1.80), those assigned to reslizumab had a lower risk (8% *versus* 11.9%; risk

ratio 0.69, 95% CI 0.44–1.09) and those assigned to benralizumab had a greater risk (13.3% versus 9.2%; risk ratio 1.46, 95% CI 0.96–2.21). As the outcome drug-related adverse events were not pre-defined, the Task Force members did not consider this outcome in the overall certainty of the evidence of effects.

Benefits

Anti-IL-5 and anti-IL-5R α therapies reduce exacerbations and hospitalisations 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-IL-5 strategy drugs were well tolerated. The frequency of adverse effects was similar when compared with placebo.

Conclusions

An anti-IL-5 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 FEV₁ 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-IL-5 drug. Uncertainty exists around the best biomarker and blood eosinophil threshold that would predict response to anti-IL-5 therapy. In addition to blood eosinophils, the efficacy of anti-IL-5 therapy depends on the degree of pre-existing 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 (age <5 years). Therefore, more evidence is needed to provide higher quality recommendations in the paediatric age group.

What others are saying

The 2019 Global Initiative for Asthma (GINA) guidelines [20] and the National Institute for Health and Care Excellence (NICE) technology appraisal guidance [21–23] include mepolizumab, reslizumab and benralizumab as add-on therapeutic options for severe eosinophilic asthma (at GINA step 5).

ERS/ATS recommendation

We suggest an anti-IL-5 strategy as add-on therapy for adult patients with severe uncontrolled asthma with an eosinophilic phenotype and for those with severe corticosteroid-dependent asthma (the Task Force gave this a conditional recommendation because inclusion criteria across studies did not consistently align 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-IL-5 and anti-IL-5R α strategy drugs [24]. Due to the limited number of treated adolescents or children, the Task Force was unable to provide a recommendation for the use of anti-IL-5 and anti-IL-5R α antibodies in this age group.

Question 2: Should a measurement of a specific biomarker be used to guide initiation of treatment with a monoclonal anti-IL-5 or IL-5R α antibody in adults and children with severe asthma? (Chosen biomarkers being F_{ENO}, peripheral or sputum eosinophils and serum periostin)

Summary of the evidence

We identified 12 randomised controlled trials of anti-IL-5 therapies in children and adults 12–75 years of age that evaluated differential response to therapy among subgroups of individuals with higher or lower levels of eosinophils in blood or sputum in *post hoc* analyses [10–17, 19, 25, 26]. One study was a meta-analysis of two randomised controlled trials of mepolizumab's therapeutic responsiveness combining the 100 mg *s.c.* and 75 mg intravenous doses for the analysis by blood eosinophil level [26]. Notably, four of the studies recruited only subjects with evidence of eosinophilic asthma, defined as sputum eosinophils $\geq 3\%$ or blood eosinophil level $\geq 300 \mu\text{L}^{-1}$ [11–13, 25]. Six of the studies included children age ≥ 12 years [10, 11, 13, 15, 17, 26]. 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-IL-5 strategy [27].

Cut-offs assessed for baseline blood eosinophil levels, and hence the definition of what constitutes eosinophilia, varied across anti-IL-5 strategies. Studies of mepolizumab specifically assessed a cut-off of blood eosinophils $\geq 150 \mu\text{L}^{-1}$. For mepolizumab, there was a 73% (95% CI -82–-59%) reduction in exacerbations among those with a blood eosinophil level $\geq 500 \mu\text{L}^{-1}$ compared with a 36–39% reduction in all other groups with eosinophil levels $\geq 150 \mu\text{L}^{-1}$. Notably, subjects with eosinophil levels $\geq 150 \mu\text{L}^{-1}$ constituted nearly three-quarters of the severe asthma population in those studies. Patients treated with reslizumab with a baseline eosinophil level $\geq 400 \mu\text{L}^{-1}$ had a 54% reduction in exacerbations; higher cut-offs were not associated with a greater reduction in exacerbations. For benralizumab, a cut-off $\geq 300 \mu\text{L}^{-1}$ 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 $< 300 \mu\text{L}^{-1}$ experienced a reduction in exacerbations.

For effects on asthma control and quality of life, the data again varied by anti-IL-5 strategy; among those with a baseline eosinophil level $\geq 150 \mu\text{L}^{-1}$, 63% treated with mepolizumab *versus* 41% treated with placebo achieved a ≥ 0.5 -point reduction from baseline in ACQ-5 (risk ratio 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 $\geq 500 \mu\text{L}^{-1}$). For benralizumab, only subjects with a baseline eosinophil level $\geq 300 \mu\text{L}^{-1}$ experienced a significant improvement in asthma control, assessed as change in ACQ-6 score from baseline (mean difference -0.28 points, 95% CI -0.41–-0.15 points), whereas those with an eosinophil level $< 300 \mu\text{L}^{-1}$ did not (mean difference -0.20 points, 95% CI -0.44–0.3 points). Similarly for reslizumab, a cut-off eosinophil level $\geq 400 \mu\text{L}^{-1}$ was associated with improved asthma control (mean difference in ACQ-7) from baseline -0.27 points (95% CI -0.36–-0.19 points), whereas those with an eosinophil level $< 400 \mu\text{L}^{-1}$ did not have a significant benefit (-0.12 points, 95% CI -0.33–0.09 points). Sputum eosinophil level was only considered in one study of reslizumab [12] and sputum levels were categorised as $\geq 10\%$ 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 *i.v.* reslizumab in patients previously treated with 100 mg *s.c.* mepolizumab [27]. It reported that persistently high levels of eosinophils (blood $> 300 \mu\text{L}^{-1}$ and sputum $> 3\%$) after treatment with mepolizumab characterised 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 manifest by a high sputum or blood eosinophil level, may be useful in determining which subjects may benefit from additional anti-IL-5 strategies; however, this requires further confirmation.

Benefits

The specific cut-off blood eosinophil count to predict improved asthma control and reduction in exacerbations varies across anti-IL-5 strategies. However, there is very low quality evidence that mepolizumab may provide further benefit in reducing exacerbations in patients with baseline blood eosinophilia $\geq 500 \mu\text{L}^{-1}$ compared with those with eosinophil levels < 150 , 150 – < 300 and 300 – $< 500 \mu\text{L}^{-1}$.

Harms

There were five studies 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 among those with higher *versus* lower eosinophil counts for benralizumab. For reslizumab, only subjects with baseline eosinophilia $\geq 400 \mu\text{L}^{-1}$ 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 with patients with baseline eosinophilia $\geq 400 \mu\text{L}^{-1}$. There was a 5% reduction in the number of adverse events among those with an eosinophil count $\geq 400 \mu\text{L}^{-1}$ 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 [28, 29].

Other considerations

Most of the studies focused on blood eosinophils as a biomarker, and there were limited data on sputum eosinophils and no data on F_{ENO} or serum periostin. Blood eosinophils can be measured in any standard laboratory, increasing its feasibility as a biomarker; however, additional testing beyond the point of care may be 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

specialised centres. It should be noted that there may be causes other than atopy (e.g. parasitic infections) for peripheral blood eosinophilia, especially in low- and middle-income settings.

Cut-offs to assess response varied across studies of anti-IL-5 medications and there were no data comparing therapeutic regimens using different cut-off levels. Finally, most of the anti-IL-5 strategies use a fixed-dose regimen based on randomised controlled trial data suggesting a plateau in the dose response; however, one study suggested that persistent eosinophilia, despite anti-IL-5 strategies, should be considered as an opportunity to add-on reslizumab using a weight-adjusted dose regimen [27].

Conclusions and research needs

Although the data suggest that subjects with higher levels of blood eosinophil counts benefit more from anti-IL-5 strategies, the evidence we reviewed does not show that a specific level of blood eosinophils $\geq 150 \mu\text{L}^{-1}$ for mepolizumab, $\geq 300 \mu\text{L}^{-1}$ for benralizumab and $\geq 400 \mu\text{L}^{-1}$ 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 corticosteroid and ICS. It is not known if eosinophil levels obtained during periods of asthma exacerbation are better predictors of treatment response when compared with those measured during periods of clinical stability. Future studies should focus on developing additional noninvasive biomarkers for adults and children that can be used at point of care to predict responsiveness to different anti-IL-5 strategies.

What others are saying

The 2019 GINA guidelines [20] recommend the use of an anti-IL-5 and anti-IL-5R α strategy for patients who remain uncontrolled despite step 4 or 5 therapy who have blood eosinophils $\geq 300 \mu\text{L}^{-1}$.

ERS/ATS recommendation

We suggest that a blood eosinophil count cut-off point $\geq 150 \mu\text{L}^{-1}$ can be used to guide anti-IL-5 initiation in adult patients with severe asthma and a history of prior asthma exacerbations (conditional recommendation, low quality evidence).

Remarks

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

Question 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 F_{ENO} , peripheral or sputum eosinophils and serum periostin)

Summary of the evidence

We identified three randomised, double-blind placebo-controlled trials [31–33] which recruited participants age 12–75 years. Of these, two studies [32, 33] involving 1014 eligible participants formed the evidence for the Task Force recommendations. These two trials included individuals with uncontrolled asthma. In one study [33], patients had uncontrolled symptoms while taking an ICS with or without a controller. In the other study [32], only participants with severe persistent asthma were recruited, whose asthma remained uncontrolled despite ICS and a long-acting β_2 -agonist (LABA).

In both trials, eligible participants were randomised 1:1 to receive omalizumab or placebo. Omalizumab dose was determined on the basis of pre-treatment serum total IgE level ($\text{IU}\cdot\text{mL}^{-1}$) and body weight (kg) according to the European [33] or ATS [32] omalizumab dosing table, which ensured a minimum omalizumab dose of $0.008 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{IgE}^{-1}$ ($\text{IU}\cdot\text{mL}^{-1}$) every 2 weeks or a minimum of $0.016 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{IgE}^{-1}$ ($\text{IU}\cdot\text{mL}^{-1}$) every 4 weeks.

BUSSE *et al.* [33] pre-planned an analysis that divided participants into two subgroups according to eosinophil counts at screening: low ($<300 \mu\text{L}^{-1}$) and high ($\geq 300 \mu\text{L}^{-1}$). A subgroup analysis was performed by HANANIA *et al.* [32], which divided participants into high and low subgroups as: F_{ENO} low <19.5 ppb, high ≥ 19.5 ppb; peripheral blood eosinophils low $<260 \mu\text{L}^{-1}$, high $\geq 260 \mu\text{L}^{-1}$; and serum periostin levels low $<50 \text{ ng}\cdot\text{mL}^{-1}$, high $\geq 50 \text{ ng}\cdot\text{mL}^{-1}$.

Pooling of the data from the two studies was not possible. In BUSSE *et al.* [33], there were significant improvements in exacerbation rates (hazard ratio 0.41, 95% CI 0.20–0.84) and a clinically trivial but

statistically significantly greater change in FEV₁ % pred at 24 weeks (mean difference 7.35, 95% CI 1.38–13.31) with omalizumab compared with placebo in patients with a high eosinophil count, whereas there were no differences in patients with low eosinophils (<300 μL^{-1}). In the study by HANANIA *et al.* [32], there was a significantly longer time to first asthma exacerbation with omalizumab compared with placebo in patients with high ($\geq 260 \mu\text{L}^{-1}$) eosinophil count at 48 weeks follow-up (hazard ratio 0.64, 95% CI 0.48–0.85), whereas there were no differences in patients with low (<260 μL^{-1}) eosinophil count (hazard ratio 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 with placebo in patients with high ($\geq 260 \mu\text{L}^{-1}$) eosinophils (mean difference 0.14 points, 95% CI –0.11–0.30 points), while there was a small statistically, but not clinically significant, difference in the low (<260 μL^{-1}) eosinophil subgroup (mean difference 0.26 points, 95% CI 0.06–0.46 points).

In the subgroup analysis by F_{ENO} [32], there was a significant relative reduction of exacerbation rates with omalizumab compared with placebo in patients with high (≥ 19.5 ppb) F_{ENO} at 48 weeks follow-up (53%, 95% CI 37–70%), whereas there were no differences for those patients with low (<19.5 ppb) F_{ENO} (16%, 95% CI –32–46%). The time to first asthma exacerbation with omalizumab, compared with placebo, was significantly longer in patients with high (≥ 19.5 ppb) F_{ENO} at 48 weeks follow-up (hazard ratio 0.38, 95% CI 0.24–0.60), whereas there were no differences in patients with low (<19.5 ppb) F_{ENO} (hazard ratio 1.00, 95% CI 0.62–1.61). There were also larger changes of mean AQLQ with omalizumab compared with placebo in high (≥ 19.5 ppb) F_{ENO} patients at 48 weeks of follow-up (mean difference 0.39 points, 95% CI 0.06–0.72 points), whereas there were no differences in low (<19.5 ppb) F_{ENO} patients (mean difference 0.24 points, 95% CI –0.09–0.57 points).

There were no differences in the relative reduction of exacerbation rates at 48 weeks or FEV₁ when omalizumab was compared with placebo in periostin high ($\geq 50 \text{ ng}\cdot\text{mL}^{-1}$) or low (<50 $\text{ng}\cdot\text{mL}^{-1}$) patients [32]. However, compared with placebo, omalizumab improved AQLQ in patients with low (<50 $\text{ng}\cdot\text{mL}^{-1}$) periostin levels at 48 weeks follow-up (mean difference 0.50 points, 95% CI 0.22–0.78 points), whereas there were no differences in patients with high ($\geq 50 \text{ ng}\cdot\text{mL}^{-1}$) serum periostin levels (mean difference 0.10 points, 95% CI –0.19–0.39 points).

Benefits

In patients treated with omalizumab compared with placebo, the presence of a baseline blood eosinophil count $\geq 260 \mu\text{L}^{-1}$ is associated with greater improvements in FEV₁, and a decreased rate of exacerbations as well as longer time to first exacerbation, compared with those with a blood eosinophil count <260 μL^{-1} .

In patients treated with omalizumab compared with placebo, the presence of $F_{\text{ENO}} \geq 19.5$ ppb is associated with improvements in AQLQ, reduced exacerbation rate and longer time to first exacerbation compared with those with $F_{\text{ENO}} < 19.5$ ppb. In patients treated with omalizumab compared with placebo, the presence of periostin <50 $\text{ng}\cdot\text{mL}^{-1}$ was associated with improvements in AQLQ compared with those with periostin $\geq 50 \text{ ng}\cdot\text{mL}^{-1}$. 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 [34].

Harms

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

Other considerations

The estimates of effect included one single study (meta-analysis of the two randomised controlled trial was not possible), which introduced some uncertainty due to the limited number of patients included in each subgroup according to the biomarker 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.

Conclusions and research needs

Blood eosinophil counts and F_{ENO} 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 with placebo. There were no differences in adverse effects based on the high and low biomarker subgroups, suggesting that the high blood eosinophil and high F_{ENO} patients achieve clinical benefit without additional adverse effects, whereas low biomarker 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 eosinophils to select patients most likely to respond to omalizumab. Of particular note is the study by CASALE *et al.* [35], who

reported an analysis that pooled the results of two randomised controlled trials. The studies by BUSSE *et al.* [36] and SOLER *et al.* [37] were both phase 3, double-blind placebo-controlled trials, comprising a total of 1071 participants comparing omalizumab with placebo in participants with moderate to severe asthma. The pooled analysis published in 2018 investigated the annualised exacerbation rates in the omalizumab group *versus* placebo according to the subgroups of blood eosinophils: high ($\geq 300 \mu\text{L}^{-1}$) and low ($< 300 \mu\text{L}^{-1}$) [35]. The results support the recommendations of the Task Force. There was a more pronounced reduction in exacerbations rates in the omalizumab *versus* placebo group for the high biomarker subgroup, *i.e.* for those with an eosinophil count $\geq 300 \mu\text{L}^{-1}$ there was a 67% reduction in exacerbations compared with a 45% reduction in the $< 300 \mu\text{L}^{-1}$ 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 high biomarker (eosinophil count $\geq 300 \mu\text{L}^{-1}$) group *versus* 58.1% (95% CI 52.7–63.4%) in the low biomarker group (eosinophil count $< 300 \mu\text{L}^{-1}$) [38].

Future randomised controlled trials should evaluate baseline blood eosinophils and F_{ENO} 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 2019 GINA guidelines [20] state that blood eosinophil level $\geq 260 \mu\text{L}^{-1}$ and $F_{\text{ENO}} \geq 20$ ppb are factors that may predict a good response to treatment.

Neither the 2019 British Thoracic Society/Scottish Intercollegiate Guidelines Network (BTS/SIGN) [39] nor the NICE asthma guidelines [30] make comment about predictor biomarkers for anti-IgE treatment response.

ERS/ATS recommendations

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

- Using a blood eosinophil cut-off $\geq 260 \mu\text{L}^{-1}$ 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 F_{ENO} cut-off ≥ 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 F_{ENO} values below the proposed cut-offs can still benefit from omalizumab. In addition, these thresholds were largely determined by one particular study [32]. Periostin was omitted from these recommendations, as this biomarker is not clinically available and it is not useful in children age < 12 years because it is also produced from growing bone.

The recommendations place a high value on an increased treatment response when blood eosinophils and F_{ENO} are used to select patients and a low value on the use of periostin.

Question 4: Should a long-acting inhaled muscarinic antagonist be used in adults and children with severe asthma?

Summary of the evidence

We identified three randomised, 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) [40–42]. These trials included individuals with severe uncontrolled asthma on GINA step 4–5 or NAEPP step 5 therapies. Adults were treated with at least high-dose ICS in combination with a LABA, while adolescents and children were treated with medium-dose ICS and a LABA with a third controller.

In the adolescent and paediatric studies, eligible patients were randomised in a 1:1:1 ratio to receive tiotropium 5 μg (2 puffs of 2.5 μg) or 2.5 μg (2 puffs of 1.25 μg) or placebo (2 puffs), each delivered for

12 weeks *via* the Respimat Soft Mist inhaler as add-on to pre-enrolment background therapy with ICS plus one or more controller therapies. Whereas two adult studies [41] compared 5 µg tiotropium (2 puffs of 2.5 µg) delivered by Respimat over 48 weeks to placebo, one adult study [40] involved an 8-week, three-way crossover design with 5 µg tiotropium (2 puffs of 2.5 µg), 10 µg tiotropium (2 puffs of 5 µg) and placebo, and was excluded from further analyses and the primary meta-analyses. The remaining four trials enrolled a total of 1433 participants (2.5 µg dose, n=528) and were pooled for meta-analyses to inform the Task Force's judgements.

Across the four parallel-arm trials including children, adolescents and adults, the addition of tiotropium 5 µg resulted in improvements in mean peak FEV₁ response compared with placebo (123 mL, 95% CI 88.2–158.7 mL), 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 µg also marginally improved ACQ-7 (–0.11 points, 95% CI –0.2–0.01 points) and prevented asthma worsening (based on exacerbations or symptoms, risk ratio 0.79, 95% CI 0.7–0.89; absolute risk 133, 95% CI 54–122, fewer worsening episodes per 1000) compared with placebo, but again, serious imprecision in the certainty estimates was noted for children and adolescents. In children and adolescents, addition of tiotropium 2.5 µg did not improve asthma control scores but did improve FEV₁ % pred (mean difference 4.99, 95% CI 2.84–7.15) and reduced asthma worsening (risk ratio 0.66, 95% CI 0.45–0.97). *Post hoc* analyses of adjusted mean trough FEV₁/forced vital capacity 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 µg did not result in significant differences in AQLQ (mean difference 0.10 points, 95% CI –0.04–0.23 points), but did increase the time to first exacerbation requiring OCS (hazard ratio for placebo 0.79, 95% CI 0.62–1.01). Asthma exacerbations requiring hospitalisation were too infrequent in both the tiotropium (16 out of 453 subjects) and placebo (20 out of 454 subjects) arms to draw conclusions [41]. The crossover study in adults [40] that was excluded from the primary analysis similarly noted beneficial effects of tiotropium 5 µg (mean difference 139 mL, 95% CI 96–181 mL) and 10 µg (mean difference 170 mL, 95% CI 128–213 mL) on peak FEV₁ response in adults.

Adverse events were less frequent in the tiotropium arms compared with placebo in these four trials (risk ratio 0.92, 95% CI 0.86–0.98). Severe adverse events were equally infrequent across treatment arms.

Benefits

Long-acting muscarinic antagonist (LAMA) treatment in children, adolescents and adults with severe asthma may improve FEV₁ and may reduce loss of asthma control. In adults, treatment with tiotropium 5 µg also improves asthma control and increases time to first exacerbation.

Harms

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

Conclusions and research needs

The addition of tiotropium improves FEV₁ 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 LAMAs (umeclidinium and glycopyrronium) currently available which could be alternative long-term bronchodilator therapies for severe asthma. Treatments with umeclidinium and glycopyrronium have beneficial effects on lung function and symptom control in individuals with mild to moderate, persistent asthma [43–45], 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 LAMAs that might benefit from the step-wise addition of muscarinic antagonists compared with alternative step-up options such as LABAs 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 LAMAs [45, 46]. Three randomised controlled trials only included subjects with FEV₁ <80% predicted. KERSTJENS *et al.* [47] showed beneficial effects in both those with screening FEV₁ <60% or 60–80% predicted. Two trials in children and adolescents enrolled asthma patients with FEV₁ 60–90% predicted [42, 48]. Hence, it is not clear whether individuals, particularly adults, with severe asthma and higher lung function on combination therapy with high-dose ICS and a LABA will benefit from the addition of a LAMA.

A responder analysis of a severe asthma trial cohort showed equally beneficial effects when comparing subgroups based on baseline lung function, age, sex, ethnicity, body mass index 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 [47]. Future trials in increasingly ethnically diverse severe asthma cohorts should provide insight into the beneficial effects of LAMAs 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

The 2019 GINA guidelines [20] 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 [49] do not outline any role for the muscarinic antagonists.

ERS/ATS 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 Task Force only found data on the efficacy of 5 µg in adults with severe asthma, the effects on lung function were similar to the FDA-approved 2.5 and 5 µg doses evaluated in parallel, placebo-controlled trials of adults with mild to moderate asthma. In addition, clinical trials in adolescents with moderate and severe asthma showed that the 2.5 and 5 µg 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 favouring the intervention. Tiotropium was considered probably acceptable and probably feasible to implement. This recommendation also accounts for the feasibility of this inhaled therapy compared with the cost and burden of alternative add-on biological therapies for severe asthma.

Question 5: 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 [1]. Since then, six randomised controlled trials have been conducted [50–55], of which five included only adults and one included only children 6–<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 (totalling 529 participants) used doses ranging from 250 to 500 mg three times per week for a treatment period of 26–48 weeks [50, 51]. The other (n=97) used a dose of 600 mg·day⁻¹ for 3 days and 600 mg·week⁻¹ thereafter for 11 weeks [53]. The clarithromycin randomised controlled trials (totalling 171 participants) used 600 mg twice daily, ranging from 8 to 16 weeks in treatment duration [54, 55]. In children (n=55), azithromycin nightly doses were given according to body weight, ranging from 250 mg for 25–40 kg and 500 mg for >40 kg for a total of 12 months (the study was prematurely terminated at 30 weeks due to lack of clinical efficacy) [52].

Compared with placebo, during 48 weeks of follow-up, azithromycin reduced the number of combined moderate and severe exacerbations (1.07 *versus* 1.86 events·patient⁻¹·year⁻¹; risk ratio 0.59, 95% CI 0.47–

0.74) [51]. 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% *versus* 34.6%; risk ratio 0.77, 95% CI 0.44–1.34) in children or adults, during a follow-up period ranging from 24 to 48 weeks [50–52]. Neither azithromycin nor clarithromycin treatment improved ACQ-7 (mean difference 0.11 points, 95% CI –0.34–0.12 points) or AQLQ (mean difference 0.16 points, 95% CI –0.06–0.37 points) in adults beyond the MCID.

Relative to placebo, treatment with azithromycin or clarithromycin in adults or children was not associated with changes in post-bronchodilator FEV₁ % pred (mean difference 1.95, 95% CI –2.42–6.32) or pre-bronchodilator FEV₁ L (mean difference 0.37, 95% CI –2.17–2.91) that reached the MCID [50, 53, 54].

The effects of clarithromycin on airway inflammation were inconsistent, with only one of two studies showing significant reductions in airway neutrophilia [55]. Compared with placebo, macrolide therapy in adults was associated with a lower number of lower respiratory tract infections requiring antibiotics (20.9% *versus* 35.6%; risk ratio 0.60, 95% CI 0.45–0.79) [50, 51].

The number of study participants with at least one adverse event (67.3% *versus* 72.2%; risk ratio 0.93, 95% CI 0.73–1.19) and the number of serious adverse events (9.1% *versus* 11.4%; risk ratio 0.81, 95% CI 0.52–1.24) in adults or children were not different from placebo [50, 51, 53, 54].

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 [51]. 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 diarrhoea; however, the number of serious adverse events or number of participants with at least one adverse event is not different to placebo. Although macrolides have a potential risk for QT prolongation or hearing loss, the frequency of these events is not reported to be higher than in the placebo arm in patients whom at baseline had no hearing deficits or abnormally prolonged corrected QT [51]. Relative to placebo, the prevalence of nasal and oropharyngeal macrolide-resistant streptococci increased in one study [50], but not in another [51]. Those treated with azithromycin for 48 weeks had reduced airway *Haemophilus 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 [51, 56].

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 have 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

The 2019 GINA guidelines [20] 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 2016 BTS/SIGN guidelines [57], the use of macrolide antibiotics in asthma was not recommended; the 2019 BTS/SIGN revised guidelines [39] do not mention the use of chronic macrolide therapy for severe asthma.

The FDA has not approved the use of chronic macrolide therapy for asthma.

ERS/ATS recommendations

We suggest a trial of macrolide treatment to reduce asthma exacerbations in adult asthma subjects 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

The recommendations are 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.

Question 6: Should a monoclonal anti-IL-4R α be used in adults and children with severe asthma?

Summary of the evidence

Dupilumab is a fully human monoclonal antibody directed against the α subunit of IL-4 receptor. It blocks signalling of two key type 2 cytokines: IL-4 and IL-13. We identified three randomised, placebo-controlled trials evaluating dupilumab as add-on therapy in patients with moderate to severe asthma [58–60]. Two randomised controlled trials included adolescent (age 12–17 years) and adult (age ≥ 18 years) participants [59, 60], and one trial included only adult participants [58].

In the phase 2b dose-ranging clinical trial [58], four dosing regimens of dupilumab were studied: 200 or 300 mg of the drug administered *s.c.* 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 randomised 1:1:1:1 into four treatment arms or placebo. The primary end-point was change in FEV₁ (L) at 12 weeks in patients with blood eosinophil counts $\geq 300 \mu\text{L}^{-1}$. Pre-specified secondary end-points at weeks 12 and 24 included asthma exacerbation rate, time to severe exacerbation, asthma symptom score, asthma quality of life and change in FEV₁ (% pred).

One phase 3 efficacy and safety randomised controlled trial [59] 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 400 mg) or 300 mg (after a loading dose of 600 mg) every 2 weeks for 52 weeks. A total of 1902 participants were randomised 2:2:1:1 with matched volume placebo. Primary end-points were annualised exacerbation rates (week 52) and absolute change in FEV₁ (week 12). Secondary end-points included change in FEV₁ % pred, ACQ and AQLQ, as well as subgroup analysis by blood eosinophil count.

The second phase 3 randomised controlled trial [60] evaluated dupilumab (300 mg every 2 weeks for 24 weeks) in 210 adolescents and adults with severe OCS-dependent asthma. After a steroid dose-optimisation period, patients were randomised 1:1 to receive dupilumab or placebo. OCS dose was adjusted down during weeks 4–20. The primary end-point was percentage reduction in OCS dose required to maintain asthma control. Secondary end-points included proportion of patients with at least 50% reduction in OCS dose and proportion of patients with reduction in OCS dose to $< 5 \text{ mg}\cdot\text{day}^{-1}$.

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 200 and 300 mg 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 or 300 mg every 2 weeks; 24 and 52 weeks) experienced substantial (46–70.5%) reductions in annualised rates of asthma exacerbations. Dupilumab therapy resulted in a greater proportion of participants with OCS-dependent severe asthma experiencing $> 50\%$ reduction in OCS dose (relative risk 1.49, 95% CI 1.22–1.83; absolute risk 26, 95% CI 12–44, more achieved 50% reduction per 100), reduction in OCS dose to $< 5 \text{ mg}\cdot\text{day}^{-1}$ (relative risk 1.92, 95% CI 1.46–2.53; absolute risk 344, 95% CI 172–572, more per 1000) and discontinuation of maintenance OCS (relative risk 1.81, 95% CI 1.28–2.57). Improvements in FEV₁, ACQ-5 and AQLQ were statistically significant, but did not reach the MCID.

The effect size for all above outcomes was larger in patients with blood eosinophil counts $\geq 300 \mu\text{L}^{-1}$ when compared with eosinophils $< 300 \mu\text{L}^{-1}$ (see evidence profiles in the supplementary material). One study further stratified the study cohort by blood eosinophils < 150 , 150–300 and $\geq 300 \mu\text{L}^{-1}$ [59]. Rate ratio for annualised 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⁻¹·year⁻¹) for the subgroup with blood eosinophils $\geq 300 \mu\text{L}^{-1}$, 0.60 (96% CI 0.43–0.83; 0.515 *versus* 0.855 events-patient⁻¹·year⁻¹) for the subgroup with blood eosinophils 150–300 μL^{-1} and 1.04 (95% CI 0.76–1.43; 0.604 *versus* 0.576 events-patient⁻¹·year⁻¹) for the subgroup with blood eosinophils $< 150 \mu\text{L}^{-1}$. The same study reported similar results for exacerbations and lung function when stratified by $F_{\text{ENO}} \geq 50$, ≥ 25 – < 50 and < 25 ppb. A *post hoc* biomarker interaction analysis found the greatest treatment response in patients with $F_{\text{ENO}} \geq 25$ ppb and blood eosinophils $\geq 150 \mu\text{L}^{-1}$.

Benefits

Dupilumab, as add-on therapy in patients with asthma that is uncontrolled on medium- to high-dose ICS and LABA, may reduce exacerbations and improve asthma symptoms and lung function. The efficacy is greater in patients with type 2 biomarkers (blood eosinophils $\geq 150 \mu\text{L}^{-1}$ or $F_{\text{ENO}} \geq 25$ ppb). Dupilumab may reduce OCS dose in patients with severe corticosteroid-dependent asthma.

Harms

The risk of dupilumab therapy appears to be small, with injection site reaction as the most common treatment-related adverse effect. Frequencies 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. As 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 [58–60]. 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 higher 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

The 2019 GINA guidelines [20] recommend dupilumab as add-on option for patients with severe eosinophilic or type 2 asthma uncontrolled on high-dose ICS and LABA, or requiring maintenance OCS.

The NICE guidelines [30] do not currently include dupilumab as an 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).

Remarks

The recommendation places 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 the limited number of adolescents treated with anti-IL-4/13, the Task Force was unable to provide a recommendation for this age group and no available evidence exists for children <12 years of age.

Discussion

The ERS/ATS Severe Asthma Task Force evaluated six 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, and the feasibility and the acceptability were all considered in developing each recommendation (table 2). A conditional recommendation was made for the use of anti-IL-5 and anti-IL-4/13 strategies for severe uncontrolled eosinophilic phenotype. Anti-IL-4/13 is also indicated for systemic corticosteroid-dependent severe asthma subjects regardless of eosinophilic status. Specific eosinophil and F_{ENO} cut-offs were recommended to identify those with the greatest likelihood of response to anti-IL-5 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 [61–63]. Stringent diagnostic requirements are imposed, *e.g.* adults smokers with asthma are often excluded to avoid an inadvertent misdiagnosis of

TABLE 2 European Respiratory Society (ERS)/American Thoracic Society (ATS) Severe Asthma Task Force recommendations for the management of severe asthma

Question	Recommendation	Strength	Quality of evidence
1	We suggest an anti-IL-5 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	Low
2	We suggest that a blood eosinophil cut-point $\geq 150 \mu\text{L}^{-1}$ can be used to guide anti-IL-5 initiation in adult patients with severe asthma and a history of prior asthma exacerbations	Conditional	Low
3	We suggest using a blood eosinophil cut-off $\geq 260 \mu\text{L}^{-1}$ 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 F_{ENO} cut-off ≥ 19.5 ppb to identify adolescents (>12 years) and adults with severe allergic asthma more likely to benefit from anti-IgE treatment	Conditional	Low
4	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
5	We suggest a trial of macrolide treatment to reduce asthma exacerbations in adult asthma subjects on GINA/NAEPP step 5 therapy that remain persistently symptomatic or uncontrolled	Conditional	Low
	We suggest against the use of chronic macrolide treatment in children and adolescents with severe uncontrolled asthma	Conditional	Low
6	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	Low

IL: interleukin; R: receptor; F_{ENO} : exhaled nitric oxide fraction; GINA: Global Initiative for Asthma; NAEPP: National Asthma Education and Prevention Program.

COPD. However, this is illogical; nonsmokers 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 [61, 63]. The first entirely logical reason would be the absence of any evidence of type 2 activity; the second, far more dubious, the presence of type 2 activation, but a coexistent disqualification such as smoking or the absence of variable airflow obstruction. The Wessex group recently evaluated 37 randomised controlled trials of type 2 biologicals and found that <10% of patients in the Wessex Severe Asthma Cohort would have been enrolled in landmark phase 3 trials of biological therapies, with commonest reasons for exclusion being failure to demonstrate either or both of fixed and variable airflow obstruction [61]. The exclusion rate for patients with eosinophilic asthma was even higher. In the accompanying editorial [64], 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 [63] and also the finding of benefit of anti-type 2 strategies in “eosinophilic COPD” [65, 66]. 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 [1]. 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 exacerbations and death. In the UK National Review of Asthma Deaths [67, 68], ~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 exacerbation, were underuse of ICS, overuse 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 such as poor adherence. However, there is 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 optimised as far as possible, but is still inadequate. It has been argued

elsewhere that such children (or other nonadherent patients) should be offered biologicals if they have the necessary treatable airway trait, to prevent asthma deaths [69, 70]. The same argument has been advanced in adults. This is not a group that is 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 nonadherent must be that it is directly observed in hospital; such patients cannot be candidates 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 [71], and although atopy is very common in severe paediatric asthma, it is by no means clear that airway eosinophilia is necessarily type 2 driven [72]. Indeed, even in adult asthma, non-type 2 eosinophilic endotypes are being discovered [73]. Also, there is reason to suppose that antieosinophil strategies may be deleterious in children, given the role of the eosinophil in immune homeostasis [74]. There are extensive paediatric data on efficacy and safety of the anti-IgE monoclonal omalizumab [75–77], so there should be no reason not to replicate these studies for other anti-IL-5 strategies, in the absence of a reliable biomarker of efficacy. In summary, it is essential to perform 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 [78].

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-IL-13 monoclonal tralokinumab [79, 80]. At least three randomised controlled studies in adults failed to show significant clinical efficacy [81–83] and there are no plans to do a paediatric trial, on the basis that the data show that the IL-13 pathway is not crucial in airway eosinophilia. It is true that adolescents age >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 exacerbation 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 F_{ENO} could offer additional information in identifying subendotypes. 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 (Severe Asthma Research Program) and U-BIOPRED (Unbiased BIOMarkers in PREDiction of respiratory disease outcomes) 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 biologicals may prove to be better on the speculation that type 2 inflammation may be most effectively abrogated by blocking all the signature type 2 cytokines, IL-4, IL-5 and IL-13, with dupilumab combined with an anti-IL-5 or anti-IL-5R α strategy. Pragmatic clinical trials may potentially provide answers to these questions for real-life clinical practice [84].

Another future challenge is the role of biologicals in low- and middle-income 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 World Health Organization defined three groups of severe asthma, of which untreated severe asthma is most relevant to low- and middle-income settings [85]. 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 low- and middle-income 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 exacerbations, where they have been very successful. In the future, they may have a role in the aftermath of

an acute asthma exacerbation. Provided the patient reaches an emergency facility in time, the basic treatment of an asthma exacerbation is straightforward. Much more difficult is to prevent a further exacerbation and it has been highlighted that the period of highest risk is in the month after the signal exacerbation [67, 68]. Given that outside the pre-school years, asthma exacerbations are caused by respiratory viral infection on the background of uncontrolled type 2-driven airway inflammation, an 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 PICO studies here have enabled the ERS/ATS Task Force to make recommendations for the treatment of severe asthma, which should lead to modifications of guidelines and improvement in outcomes that are important to patients, namely reduction in OCS dose and exacerbation frequency and improved quality of life. However, we recognise that these recommendations will not be effective across all severe asthma subjects 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 benefit. 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.

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The guidelines published by the European Respiratory Society incorporate data obtained from a comprehensive and systematic literature review of the most recent studies available at the time. Health professionals are encouraged to take the guidelines into account in their clinical practice. However, the recommendations issued by this guideline may not be appropriate for use in all situations. It is the individual responsibility of health professionals to consult other sources of relevant information, to make appropriate and accurate decisions in consideration of each patient's health condition and in consultation with that patient and the patient's caregiver where appropriate and/or necessary, and to verify rules and regulations applicable to drugs and devices at the time of prescription.

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