Evidence report for therapeutic options in severe asthma

Prepared by EBSCO Health Innovations and EBM Development Department:

Brian S. Alper, MD, MSPH, FAAFP, Vice President

Marty Mayer, DMSc, MS, PA-C, Clinical Evidence Synthesizer

Eric Manheimer, PhD, EBM Editor

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*Note that each *section* of the report also has *section-specific* page numbering at the bottom-right corner of the page. The above page numbers refer to the *report-specific* page number, which appears in bolded and italicized font in the top-right corner of the page.

Evidence report for therapeutic options in severe asthma

Part 1 - Scoping

Prepared by EBSCO Information Services

September 4, 2019

Prepared by EBSCO Health Innovations and EBM Development Department:

Brian S. Alper, MD, MSPH, FAAFP, Vice President

Martin Mayer, DMSc, MS, PA-C, Clinical Evidence Synthesizer

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Abbreviations

General abbreviations that may appear in this report

CI – confidence interval
CrI – credible interval
HR – hazard ratio
IRR – incidence rate ratio
MA – meta-analysis
MD – mean difference
NA – not applicable
NR – not reported
OR – odds ratio
RCT – randomized, controlled trial
RR – risk ratio, relative risk
RtR – rate ratio
SMD – standardized mean difference
SR – systematic review
SRMA – systematic review and meta-analysis

Abbreviations specific to this report

ACQ-7 – Asthma Control Questionnaire-7
ACT – Asthma Control Test
AQLQ – Asthma Quality of Life Questionnaire
BTS – British Thoracic Society
ERS/ATS - European Respiratory Society/American Thoracic Society
GINA – Global Initiative for Asthma
ICS – inhaled corticosteroid
LABA – long-acting β_2-agonist
LAMA – long-acting muscarinic antagonist
NVL – Nationale VersorgungsLeitlinien (German National Care Guidelines Program)
OCS – oral corticosteroid
SIGN – Scottish Intercollegiate Guidelines Network

Methods

Using an established, structured template that delineates key elements for scoping (i.e., the population, interventions, and key outcomes to consider), we collaboratively agreed with UKSH on the scope of the present evidence report. Scoping was completed on September 4, 2019.

Results – Criteria Selection for Critical Appraisal

General note about best practices with asthma:

In the interest of ensuring proper use of this decision aid and best practices with asthma, we will include a general statement in Parts 4 and 5 and the example patient decision aid regarding the importance of assuring the diagnosis of asthma is correct, as well as the following elements for optimal asthma control:

(1) avoidance of smoke (including secondhand smoke) or smoking cessation (if currently smoking),
(2) management of comorbidities and psychosocial factors (if relevant),
(3) adherence to prescribed therapies with assurance of proper inhaler technique,
(4) avoidance and/or management of allergens or allergies, asthma triggers, and air pollutants (if relevant), and
(5) implementing therapeutic exercise, activity, physiotherapy, or rehabilitation programs as appropriate.

We will also note these elements of optimal asthma care should be maximized prior to considering escalation of pharmacologic therapy. Additionally, we will note the importance of always having as-needed therapy on-hand (e.g., a short-acting β_2-agonist, or a fixed combination of low-dose inhaled corticosteroid plus formoterol if already prescribed low-dose budesonide plus formoterol or low-dose beclomethasone plus formoterol) and the importance of considering non-pharmacologic measures (e.g., in addition to (1) and (3) above, achieving or maintaining a healthy body weight and going to respiratory physiotherapy) as part of asthma management.

Population:

Inclusion criteria

Patients with severe asthma per the Global Initiative for Asthma's (GINA's) 2018 classification system[1], meaning asthma requiring treatment with therapy Steps 4 to 5 to prevent the asthma from becoming uncontrolled or asthma that remains uncontrolled despite this intensity of therapy. Steps 4 and 5 call for treatment with a medium-to-high-intensity inhaled corticosteroid plus at least one other controller medication, preferably a long-acting β_2-agonist (but in some cases, a controller agent other than a long-acting β_2-agonist might be used).

Exclusion criteria

-Patients with difficult-to-treat asthma for reasons other than having severe asthma as defined above (e.g., therapeutic non-adherence)
-Pediatric-only populations

Options:

Background therapy: Medium-to-high-intensity inhaled corticosteroid (ICS) + long-acting β2-agonist (LABA)

The baseline therapy that will serve as the intended comparator for all options shown below is medium-to-high-intensity ICS plus LABA, as each of the following options are considered "add-on" therapies to be used in conjunction with medium-to-high-intensity ICS plus LABA. Therefore, the key question this evidence report seeks to address is whether adding certain therapies to background therapy with medium-to-high-intensity ICS plus LABA makes a difference in the outcomes specified.

Please also see the note below about guidelines for asthma control and intensity of ICS therapy in asthma.

Medium-to-high-intensity ICS + LABA + long-acting muscarinic antagonist (LAMA)

The intervention is "triple therapy" with ICS plus LABA plus LAMA. Although tiotropium is no longer the only LAMA available (e.g., umeclidinium was recently approved), tiotropium will be the primary LAMA we consider due to the available evidence. If evidence considering a LAMA other than tiotropium meets inclusion criteria for this Evidence Report, then unless there is unequivocal heterogeneity of treatment effect according to medication, we may present results for LAMAs as a class.

Please also see the note below about guidelines for asthma control and intensity of ICS therapy in asthma.

*Medium-to-high-intensity ICS + LABA + anti-IgE therapy (subcutaneous omalizumab)**

The intervention is ICS plus LABA plus omalizumab.

Please also see the note below about guidelines for asthma control and intensity of ICS therapy in asthma.

*Medium-to-high-intensity ICS + LABA + anti-IL-5 therapy (other monoclonal antibodies)**

The intervention is ICS plus LABA plus anti-IL-5 monoclonal antibody, with the monoclonal antibody being any one of: mepolizumab, reslizumab, or benralizumab. Unless there is unequivocal heterogeneity of treatment effect according to medication, we may present results for anti-IL-5 therapies as a class.

Please also see the note below about guidelines for asthma control and intensity of ICS therapy in asthma.

Medium-to-high-intensity ICS + LABA + continuous low-dose oral corticosteroids (OCS)

Evidence is very limited for this option. For instance, the 2018 GINA guideline[1] only cites the 2014 European Respiratory Society and American Thoracic Society (ERS/ATS) guideline[2] for supporting evidence, which in turn notes OCS therapy is "often added as maintenance therapy in severe asthma". However, it also notes "it is not yet clear whether continuous low-dose OCS are better than multiple discontinuous bursts for controlling exacerbations" and that "optimal timing for initiation of OCS therapy has also not been defined".[2] It then discusses two very small trials of parenteral corticosteroid therapy (total sample size considering both trials = 34), but in addition to the limitations in sample size, there are also other methodologic limitations (e.g., one of the trials was published in 1991 raising uncertainty about whether it truly informs contemporary practice, and the other allowed inclusion of people already on chronic OCS therapy, to which parenteral therapy would then be added).[2-4]

Because of this, we will adopt descriptive responses only for this option, highlighting the uncertainty in the evidence and utilizing the two above-noted guidelines for descriptive content.

Please also see the note below about guidelines for asthma control and intensity of ICS therapy in asthma.

** Note about the intended comparator of medium-to-high-intensity ICS plus LABA*: For certain interventions, comparative evidence with the desired comparator (ICS plus LABA) may be mixed or lacking (e.g., although a LABA is usually the other controller therapy added to ICS prior to consideration of other therapies, some studies may allow addition of a different controller therapy prior to or instead of a LABA, such as a leukotriene receptor antagonist). If this is encountered, we may consider evidence with the closest match to the intended population, intervention, and comparator and downgrade for indirectness as warranted. If there is insufficient evidence for the desired intervention (e.g., ICS plus LABA plus omalizumab), then we may substitute evidence that keeps the background therapy the same (e.g., omalizumab vs. placebo) with the closest representation to ICS plus LABA as background therapy that is available and downgrade for indirectness as warranted.

General notes about guidelines for asthma control and intensity of ICS therapy in asthma:
We stated an *a priori* definition of severe asthma mirroring GINA 2018's definition, and this also helped inform our definition of the therapeutic options. Both GINA 2018[1] and ERS/ATS 2014[2] have a mostly similar approach to treating severe asthma: each considers the combination of an ICS and LABA to be the preferred baseline therapy, with addition of other agents not being strictly delineated in order of preference. However, GINA 2018 specifies a medium-to-high-intensity ICS in its definition of severe asthma and how it should be treated (therapy Steps 4 and 5 in GINA 2018), whereas ERS/ATS 2014 specifies a high-intensity ICS in its definition of severe asthma and its treatment. The 2018 German Nationale VersorgungsLeitlinien (NVL) guideline[5] agrees with GINA 2018 and ERS/ATS 2014 that the preferred baseline therapy in Step 4 is a combination of ICS and LABA. NVL 2018 endorses the ERS/ATS 2014 definition of severe asthma. It also recommends use of "Höchstdosis" (maximum/highest dose) ICS and LABA for Step 5 asthma therapy as well as adding a LAMA. However, for Step 4 therapy, it recommends – comparable to what GINA 2018 recommends – medium-to-high-intensity ("mittel-bis hochdosiert") ICS and LABA, or, as an alternative, medium-to-high-intensity ICS, LABA, and LAMA (an alternative also recognized by GINA 2018).

Additionally, guidelines note that, although the above may be considered the ideal therapeutic combinations, certain patients may warrant different regimens. For instance, for certain patients needing Step 4 therapy (according to GINA 2018 or NVL 2018), there may be a justification for using medium-to-high-intensity ICS and leukotriene receptor antagonist (LTRA); medium-to-high-intensity ICS, LABA, and LTRA; or medium-to-high-intensity ICS and LAMA.

From a practical and logical perspective, if a patient is already on a medium-intensity ICS and LABA and still does not have adequate asthma control, the next step – barring compelling reasons otherwise – would be to escalate the ICS dose to high-intensity. However, for some patients, this may not be desired or may be declined (e.g., tolerability). Additionally, as discussed above, there is some inconsistency with respect to whether high-intensity ICS is required to consider someone as having severe asthma. This is reflected in and may be partly explained by some inconsistency in the literature surrounding management of severe asthma. For instance, in the Cochrane review investigating the addition of anti-IL 5 therapy[6], trials often only required medium-intensity ICS therapy. For other therapies, such as LAMA and omalizumab, the trials included in systematic reviews investigating the addition of these therapies[7-9] may better represent limitation to high-intensity ICS, but still imperfectly so (e.g., Bardelas 2012 in the 2014 Cochrane review of omalizumab[8]).

Accordingly, in this evidence report, we refer to the therapeutic class of ICS as "medium-to-high-intensity ICS", recognizing there is variation in guidelines and evidence, and that the practical and logical next step for a patient on medium-intensity ICS and LABA who has inadequate asthma control is to increase the ICS to high-intensity unless there are compelling reasons to pursue a different therapeutic course.

After creation of this evidence report, the ERS/ATS released a new guideline on severe asthma.[10] Although it does not add substantially to the evidence base for the therapeutic options considered herein, it reaffirmed its 2014 definition of severe asthma (discussed above), and it did address the evidence for other therapeutic options, namely macrolide antibiotics and dupilumab, an anti-IL4Rα agent. Further information on these therapies is available in their guideline.

Outcomes:

FAQ 1: What does the treatment involve?

We will include a description of the treatment, which will include frequency of dosing and route of administration.

Descriptive responses are acceptable, and this does not involve systematic evidence searches, critical appraisal, or evidence synthesis.

FAQ 2: Will it help my symptoms?

The primary outcome of interest is asthma exacerbations requiring systemic corticosteroids, which will be assessed from randomized, controlled trials (or systematic reviews thereof). Because of the varied nature of how asthma exacerbations are reported, we will report this general outcome in 2 ways depending on availability of data: the number of patients with ≥1 exacerbation requiring systemic corticosteroids (with the corresponding relative effect estimates of odds ratios or relative risks) and the rate of exacerbations requiring systemic corticosteroids (with the corresponding relative effect estimate of rate ratio). This ultimately yields 2 related but distinct outcomes. When making comparative statements, we will state explicitly whether the comparison pertains to the outcome of ≥1 exacerbation or the rate of exacerbations requiring systemic corticosteroids.

If patient-reported outcomes for quality of life and/or asthma control are available in the sources identified for the above outcomes, we will capture these outcomes as well.

We will not report on surrogate markers for asthma control (such as change in FEV_1, PEF, or other measures obtained by spirometry or pulmonary function testing).

FAQ 3: What are the side effects?

We will report on serious adverse events and adverse events leading to discontinuation based on data from randomized, controlled trials (or systematic reviews thereof) identified as part of efforts for FAQ 2. For specific side effects considered typical for a given therapy, we will adopt descriptive responses, which may be supplemented by data from drug monographs, with side effects to consider including palpitations, upper respiratory and oropharyngeal symptoms (e.g., cough, pharyngitis, oral candidiasis), upper abdominal discomfort or gastroenteritis, injection site reaction, hypersensitivity reactions, headache, musculoskeletal symptoms (e.g., arthralgia, myalgia, lumbago), and fatigue.

If evidence reports a lower rate of adverse events with add-on therapy, this will not be considered a marker of fewer side effects, but rather, a marker of poor design or reporting of the outcome of “side effects” or “adverse events” due to the medication use.

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[10] Holguin F, Cardet JC, Chung KF, Diver S, Ferreira DS, Fitzpatrick A, Gaga M, Kellermeyer L, Khurana S, Knight S, McDonald VM, Morgan RL, Ortega VE, Rigau D, Subbarao P, Tonia T, Adcock IM, Bleecker ER, Brightling C, Boulet LP, Cabana M, Castro M, Chanez P, Custovic A, Djukanovic R, Frey U, Frankemolle B, Gibson P, Hamerlijnck D, Jarjour N, Konno S, Shen H, Vitary C, Bush A. Management of Severe Asthma: a European Respiratory Society/American Thoracic Society Guideline. Eur Respir J. 2019 Sep 26. pii: 1900588. doi: 10.1183/13993003.00588-2019. [Epub ahead of print] PubMed

Evidence report for therapeutic options in severe asthma

Part 5 - Evidence Summary

Prepared by EBSCO Information Services

September 19, 2019

Prepared by EBSCO Health Innovations and EBM Development Department:

Brian S. Alper, MD, MSPH, FAAFP, Vice President

Martin Mayer, DMSc, MS, PA-C, Clinical Evidence Synthesizer

Eric Manheimer, PhD, EBM Editor

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GINA – Global Initiative for Asthma
ICS – inhaled corticosteroid
LABA – long-acting β_2-agonist
LAMA – long-acting muscarinic antagonist
NVL – Nationale VersorgungsLeitlinien (German National Care Guidelines Program)
OCS – oral corticosteroid
SIGN – Scottish Intercollegiate Guidelines Network

Search Summary

Number of articles screened and selected

	Screened	Selected*
1st-round (DynaMed Plus)	56	4
2nd-round (Systematic review searches)	Not applicable†	
3rd-round (Study tracing)	Not applicable	
4th-round (Original article searches)	39	0
5th-round (Additional sources/updates)‡	1	1
Total	*96*	*5*

* Number shown is after deduplication

† Instead of searching for additional systematic reviews, we searched for trials published after the close of the search window in each respective systematic review. These searches are documented in 4th-round searching.

‡ After our report was finished and submitted to Universitätsklinikum Schleswig-Holstein (UKSH), UKSH provided feedback, including noting a recently-published guideline from the European Respiratory Society and American Thoracic Society (ERS/ATS 2019). ERS/ATS 2019 was published in online-ahead-of-print format on September 26, with a MEDLINE® EDAT/*entrez* of September 29, so this would not be expected to show in any of our searches. Nevertheless, we included a brief appraisal of this guideline in Critical Appraisal at the request of UKSH, so it constitutes a 5th-round source and is documented here as such.

	Articles selected for evaluation (Author Year)
Systematic reviews	4 (Farne 2017, Kew 2016, Normansell 2014, Sobieraj 2018)
Randomized, controlled trials	0
Other article types (e.g., observational studies, guidelines)	1 (ERS/ATS 2019)

Results

General note about add-on therapies in severe asthma:

Depending on the specifics of a given patient, certain add-on therapies may be more or less appropriate. For example, clinicians may reserve consideration of omalizumab for patients with severe IgE-mediated allergic asthma, and they may reserve consideration of anti-IL 5 therapy for patients with severe eosinophilic asthma/severe asthma with an eosinophilic asthma type. In some cases, licensed use of these agents may be tied to such specifics. It is expected that clinicians utilizing this evidence report will incorporate appropriate clinical judgment, only discussing/considering with the patient those options that are considered appropriate based on the patient's clinical profile.

FAQ 1: What does the treatment involve?

General notes about asthma control and guidelines for asthma control

General notes about asthma control:

In addition to assuring the diagnosis of asthma is correct, the following elements are essential for optimal asthma control:

(1) avoidance of smoke (including secondhand smoke) or smoking cessation (if currently smoking),
(2) management of comorbidities and psychosocial factors (if relevant),
(3) adherence to prescribed therapies with assurance of proper inhaler technique,
(4) avoidance and/or management of allergens or allergies, asthma triggers, and air pollutants (if relevant), and
(5) implementing therapeutic exercise, activity, physiotherapy, or rehabilitation programs as appropriate.

Prior to escalating pharmacologic treatment of asthma, the above elements should be optimized.

Additionally, regardless of what someone's asthma control regimen is, s/he should always have as-needed therapy on-hand (e.g., a short-acting β2-agonist, or a fixed combination of low-dose inhaled corticosteroid plus formoterol if already prescribed low-dose budesonide plus formoterol or low-dose beclomethasone plus formoterol). Furthermore, it is also important to consider non-pharmacologic measures as part of asthma management (e.g., items (1), (2), (4), and (5) above).

General notes about guidelines for asthma control and intensity of inhaled corticosteroid therapy in asthma:

As noted in Scoping, we stated an *a priori* definition of severe asthma mirroring GINA 2018's definition, and this also helped inform our definition of the therapeutic options. Both the 2018 Global Initiative for Asthma (GINA) and 2014 European Respiratory Society/American Thoracic Society (ERS/ATS) guidelines have a mostly similar approach to treating severe asthma: each considers the combination of an inhaled corticosteroid (ICS) and a long-acting β_2-agonist (LABA) to be the preferred baseline therapy, with addition of other agents not being strictly delineated in order of preference. However, GINA 2018 specifies a medium-to-high-intensity ICS in its definition of severe asthma and how it should be treated (therapy Steps 4 and 5 in GINA 2018), whereas ERS/ATS 2014 specifies a high-intensity ICS in its definition of severe asthma and its treatment. The 2018 German Nationale VersorgungsLeitlinien (NVL) guideline agrees with GINA 2018 and ERS/ATS 2014 that the preferred baseline therapy in Step 4 is a combination of ICS and LABA. NVL 2018 endorses the ERS/ATS 2014

definition of severe asthma. It also recommends use of Höchstdosis (maximum/highest dose) ICS and LABA for Step 5 asthma therapy as well as adding a LAMA. However, for Step 4 therapy, it recommends – comparable to what GINA 2018 recommends – medium-to-high-intensity ("mittel-bis hochdosiert") ICS and LABA, or, as an alternative, medium-to-high-intensity ICS, LABA, and LAMA (an alternative also recognized by GINA 2018).

Additionally, guidelines note that, although the above may be considered the ideal therapeutic combinations, certain patients may warrant different regimens. For instance, for certain patients needing Step 4 therapy (according to GINA 2018 or NVL 2018), there may be a justification for using medium-to-high-intensity ICS and leukotriene receptor antagonist (LTRA); medium-to-high-intensity ICS, LABA, and LTRA; or medium-to-high-intensity ICS and LAMA.

From a practical and logical perspective, if a patient is already on a medium-intensity ICS and LABA and still does not have adequate asthma control, the next step – barring compelling reasons otherwise – would be to escalate the ICS dose to high-intensity. However, for some patients, this may not be desired or may be declined (e.g., tolerability). Additionally, as discussed above, there is some inconsistency with respect to whether high-intensity ICS is required to consider someone as having severe asthma. This is reflected in and may be partly explained by some inconsistency in the literature surrounding management of severe asthma. For instance, in the Cochrane review investigating the addition of anti-IL 5 therapy (Farne 2017), trials often only required medium-intensity ICS therapy. For other therapies, such as LAMA and omalizumab, the trials included in systematic reviews investigating the addition of these therapies (Kew 2016, Normansell 2014, Sobieraj 2018) may better represent limitation to high-intensity ICS, but still imperfectly so (e.g., Bardelas 2012 in Normansell 2014).

Accordingly, in this evidence report, we refer to the therapeutic class of ICS as "medium-to-high-intensity ICS", recognizing there is variation in guidelines and evidence, and that the practical and logical next step for a patient on medium-intensity ICS and LABA who has inadequate asthma control is to increase the ICS to high-intensity unless there are compelling reasons to pursue a different therapeutic course.

After creation of this evidence report, the ERS/ATS released a new guideline on severe asthma (ERS/ATS 2019). Although it does not add substantially to the evidence base for the therapeutic options considered herein, it reaffirmed its definition of severe asthma (discussed above), and it did address the evidence for other therapeutic options, namely macrolide antibiotics and dupilumab, an anti-IL4Rα agent. Further information on these therapies is available in their guideline.

(DynaMed 2018, ERS/ATS 2014, ERS/ATS 2019, Farne 2017, GINA 2018, Kew 2016, Normansell 2014, NVL 2018, Sobieraj 2018)

For descriptive summaries of what the treatment involves, we first describe medium-to-high-intensity ICS + LABA, as this is used as the "cornerstone" baseline therapy for severe asthma and serves as the control group for studies informing this report. Thereafter, we only describe the therapy being considered as an addition to medium-to-high-intensity ICS + LABA, because this is the key question this report addresses (i.e., "What does adding X to ICS + LABA do?"). We consider it unhelpful to repeat the information for medium-to-high-intensity ICS + LABA in each category even though the implicit assumption is the agent in consideration is being added to background ICS + LABA therapy. References are provided at the end of this section rather than after each option given the shared sources used.

Background therapy: Medium-to-high-intensity ICS + LABA

Descriptive Summary

This medicine combination is often given via a single inhaler that has both medications in it. However, some people may use two separate inhalers. There are different formulations available for each medication; for example, the ICS may be budesonide or fluticasone, and the LABA may be salmeterol or formoterol. Depending on the specific combination of medication, a person may only need to use the inhaler once a day, but it is common to have to use the inhaler (or inhalers) twice a day.

LAMA (added to medium-to-high-intensity ICS + LABA)

Descriptive Summary

The addition of a LAMA is often done via a separate inhaler, but there is a newer inhaler that combines all three medications into one inhaler. A LAMA is typically inhaled once a day, but there are LAMAs that require inhalation twice a day.

Anti-IgE therapy (subcutaneous omalizumab) (added to medium-to-high-intensity ICS + LABA)

Descriptive Summary

Omalizumab is given via an injection under the skin (subcutaneous injection) every 2 to 4 weeks. The frequency is based on a person's body weight and a blood test prior to treatment (pre-treatment total serum IgE levels), and it may be adjusted if a person's weight changes substantially during treatment.

Anti-IL-5 therapy (benralizumab, mepolizumab, or reslizumab) (added to medium-to-high-intensity ICS + LABA)

Descriptive Summary

All three of the anti-IL-5 therapies are given via injection, but two (benralizumab, mepolizumab) are given under the skin and one (reslizumab) is given in the vein. Two (mepolizumab, reslizumab) are given every 4 weeks and one (benralizumab) is given every 4 weeks for the first 3 doses and is then given once every 8 weeks.

Continuous low-dose OCS (added to medium-to-high-intensity ICS + LABA)

Descriptive Summary

Continuous low-dose oral corticosteroid therapy is often taken daily, though it may be given every other day. The recommended dose is generally ≤ 7.5 mg oral prednisone (or equivalent).

(DynaMed 2018, DynaMed 2019, GINA 2018)

FAQ 2: Will it help my symptoms?

Background information about the ACQ-7 and AQLQ scales

The 7-item Asthma Control Questionnaire (ACQ-7) and Asthma Quality of Life Questionnaire (AQLQ) are commonly used to assess asthma symptom control and asthma-related quality of life. The scales are comprised as follows:

- ACQ-7: A 7-item questionnaire based on 5 asthma symptom-related questions (nighttime awakening, symptom severity on waking, activity limitations, shortness of breath, and wheezing, all based on 1-week recall), 1 question about frequency of rescue short-acting bronchodilator use in the past week, and a measurement of percent predicted FEV1 by a clinician during a visit. Final scores range from 0 to 6, with lower scores being *better*.
- AQLQ: A 32-item questionnaire based on 11 questions pertaining to activity limitations (5 of which are individualized to the patient), 12 questions pertaining to symptoms, 5 questions pertaining to emotional function, and 4 questions pertaining to environmental exposure. All items are based on 2-week recall. Final scores range from 1 to 7, with lower scores being *worse*.

As indicated by their names, these scales are considered to assess symptom control and asthma-related quality of life. However, treating ACQ-7 as though it is rigidly "distinct" from AQLQ (e.g., treating ACQ-7 as though it assesses asthma symptom control but offers no insight into asthma-related quality of life and AQLQ as though it assesses asthma-related quality of life but offers no insight into asthma symptom control) seems inappropriate; indeed, there is a considerable degree of overlap in what these questionnaires assess. Additionally, in practical execution, the concepts of asthma symptom control and asthma-related quality of life are closely interrelated. As such, in the Evidence Summary section, we use the terminology "asthma symptom control/quality of life" when summarizing research findings, and in our bolded synthesis statements, we use the phrase "asthma symptom control or quality of life".

Medium-to-high-intensity ICS + LABA + LAMA vs. medium-to-high-intensity ICS + LABA

*Articles Critically Appraised:**

Certainty	Systematic reviews	Randomized trials	Other article types
High	Kew 2016†, Sobieraj 2018‡		
Moderate			
Low	Sobieraj 2018¶		
Very low	Kew 2016**, Sobieraj 2018††		
Unusable			
Not used	Kew 2016‡‡		

* Sources not shown are not relevant for the outcome and/or comparison of interest. A synthesis of inter-related outcomes (AQLQ score, ACQ-7 score, AQLQ responder, ACQ-7 responder) results in Moderate certainty for the general outcome of asthma control/asthma-related quality of life.
† For outcome AQLQ score
‡ For outcome ACQ-7 score
¶ For outcome AQLQ responder
** For outcome exacerbations requiring oral corticosteroids (number per patient)
†† For outcomes exacerbations requiring oral corticosteroids (patients with >1 exacerbation) and ACQ-7 responder
‡‡ For outcomes exacerbations requiring oral corticosteroids (patients with >1 exacerbation) and ACQ-7 score and responder, because Sobieraj 2018 provides more current data.

Quantitative Evidence Review and Evidence Synthesis Synopsis:

Effects of LABA + ICS + tiotropium bromide vs. LABA + ICS alone (Kew 2016, Sobieraj 2018)

Outcome	No of patients (studies)	Effect size (95% CI)	Certainty (reason for downgrade)
exacerbations requiring oral corticosteroids (number per patient) (Kew 2016)	907 (2)	rate ratio 0.79 (95% CI 0.53 to 1.17)	Very low (inconsistency, such imprecision that one cannot suggest either effect or no important effect as more likely)
exacerbations requiring oral corticosteroids (patients with ≥ 1 exacerbation) (Sobieraj 2018)	1,299 (3)	risk ratio 0.84 (95% CI 0.57 to 1.22)	Very low (such imprecision that one cannot suggest either effect or no important effect as more likely)
asthma symptom control/quality of life, as assessed by ACQ-7 and AQLQ scores, including responder analyses (Kew 2016, Sobieraj 2018)	907 (2) to 1,301 (3) across 4 meta-analyses	preponderance of data suggesting little to no effect (additional detail in Part 4)	Moderate (due to inconsistency across specific effect measures and outcomes)

Evidence Summary:

We do not have enough evidence to know whether people taking a LAMA in addition to ICS + LABA therapy have a similar, higher, or lower rate of exacerbations requiring corticosteroids compared to people taking ICS + LABA therapy alone. (Very low certainty)

We do not have enough evidence to know whether people taking a LAMA in addition to ICS + LABA therapy have a similar, higher, or lower risk of having one or more exacerbations requiring corticosteroids compared to people taking ICS + LABA therapy alone. (Very low certainty)

There may be little to no difference in overall asthma symptom control or quality of life when taking a LAMA in addition to ICS + LABA therapy compared to taking ICS + LABA alone. (Moderate certainty)

Medium-to-high-intensity ICS + LABA + anti-IgE therapy (subcutaneous omalizumab) vs. medium-to-high-intensity ICS + LABA

Articles Critically Appraised:*

Certainty	Systematic reviews	Randomized trials	Other article types
High			
Moderate	Normansell 2014		
Low			
Very low			
Unusable			
Not used			

*Sources not shown are not relevant for the outcome and/or comparison of interest

Quantitative Evidence Review and Evidence Synthesis Synopsis:

Effects of LABA + ICS + omalizumab (subcutaneous) versus LABA + ICS alone (Normansell 2014)

Outcome	No of patients (studies)	Effect size (95% CI)	Certainty (reason for downgrade)
exacerbations requiring oral steroids (number per patient)	314 (1)*	rate ratio 0.66 (95% CI 0.45 to 0.97)	Moderate (imprecision[1])
asthma symptom control/quality of life, as assessed by change from baseline in AQLQ scores (AQLQ 7-point scale from 1 to 7; lower scores are worse)	246 (1)	mean difference 0.26 (95% CI 0.05 to 0.47)	Moderate (indirectness[2])

* Hanania 2011 conducted a trial of adding omalizumab to background asthma therapy comprised of at least high-dose ICS and LABA. They used a stratified randomization mechanism, and background asthma therapy was part of the stratified randomization, specifically whether the patient was taking ICS + LABA alone, ICS + LABA + one other controller therapy that was not oral corticosteroids, or ICS + LABA + oral corticosteroids. The group taking ICS + LABA alone constituted 37% of the patient sample, so with 848 patients providing data for the analysis of the rate ratio, 314 were taking ICS + LABA alone as background therapy.

[1] We did not assign a downgrade for risk of bias despite this being a subgroup of the patients in Hanania 2011, because Hanania 2011 used stratified randomization (see above footnote). However, we did assign a downgrade for imprecision given the upper bound of the confidence interval for the rate ratio is 0.97, which is compatible with clinically-negligible effects. For instance, even if a patient were having 6 exacerbations requiring corticosteroids every 6 months, the rate ratio of 0.97 means omalizumab may only bring this down to 5.82 exacerbations requiring corticosteroids every 6 months.

[2] In Holgate 2004a trial analyzed for this outcome, only about 45% of included patients were reported to be on LABA at baseline.

Because the confidence interval for the rate of exacerbations requiring oral corticosteroids suggests clearly meaningful differences and differences of questionable importance, we emphasize the confidence interval rather than the point estimate.

Evidence Summary:

People who take omalizumab in addition to ICS + LABA therapy may have fewer exacerbations requiring steroids compared to people who take ICS + LABA therapy alone. The effect may be very small, or it may reduce the number of exacerbations requiring steroids by about one-half. (Moderate certainty)

There may be little to no difference in overall asthma symptom control or quality of life when taking omalizumab in addition to ICS + LABA therapy compared to taking ICS + LABA alone. (Moderate certainty)

Medium-to-high-intensity ICS + LABA + anti-IL-5 therapy vs. medium-to-high-intensity ICS + LABA

Articles Critically Appraised:*

Certainty	Systematic reviews	Randomized trials	Other article types
High	Farne 2017		
Moderate			
Low			
Very low			
Unusable			
Not used			

*Sources not shown are not relevant for the outcome and/or comparison of interest

Quantitative Evidence Review and Evidence Synthesis Synopsis:

Effects of benralizumab + LABA + ICS (subcutaneous) versus LABA + ICS alone (Farne 2017)*

Outcome	No of patients (studies)	Effect size (95% CI)	Certainty (reason for downgrade)
exacerbations requiring systemic corticosteroids (number per patient)	2,456 (3)	rate ratio 0.62 (95% CI 0.55 to 0.70)	High
asthma symptom control/quality of life (ACQ-7 continuous; 7-point scale from 0 to 6, with lower scores being better)†	2,359 (3)	mean difference -0.20 (95% CI -0.29 to -0.11)	High
asthma symptom control/quality of life (AQLQ continuous; 7-point scale from 1 to 7, with lower scores being worse)†	1,541 (3)	mean difference 0.23 (95% CI 0.11 to 0.35)	High

* Effect estimates for the other anti-IL-5 therapies were consistent with the effect estimate for benralizumab subcutaneous, and the trials for benralizumab subcutaneous matched the desired background therapy (LABA + ICS), so we limited consideration to benralizumab subcutaneous

† A change of ≥ 0.5 was reported to be considered the minimum clinically significant difference for both the ACQ and AQLQ scores.

For the outcome of exacerbations requiring oral corticosteroids (number per patient), because our evidence synthesis for omalizumab presented the results of the confidence interval, we adopt the same approach here for purposes of seeing the relative comparison.

Evidence Summary:

Compared to people taking ICS + LABA alone, people who take anti-IL-5 therapy in addition to ICS + LABA therapy will likely reduce their number of exacerbations requiring steroids by about one-third to one-half. (High certainty)

There is likely little to no difference in overall asthma symptom control or quality of life when taking anti-IL-5 therapy in addition to ICS + LABA therapy compared to taking ICS + LABA alone. (High certainty)

Medium-to-high-intensity ICS + LABA + continuous low-dose oral corticosteroids (OCS) vs. medium-to-high-intensity ICS + LABA

Descriptive summary

As noted in Part 1 Scoping, evidence is very limited concerning the addition of continuous low-dose oral corticosteroids. For instance, the 2018 GINA guideline only cites the 2014 ERS/ATS guideline for supporting evidence, which in turn notes OCS therapy is "often added as maintenance therapy in severe asthma". However, it also notes "it is not yet clear whether continuous low-dose OCS are better than multiple discontinuous bursts for controlling exacerbations" and that "optimal timing for initiation of OCS therapy has also not been defined". It then discusses two very small trials (Ogirala 1991, ten Brinke 2004) investigating parenteral corticosteroid therapy (total sample size considering both trials = 34), but in addition to the limitations in sample size, there are also other methodologic limitations (e.g., one of the trials was published in 1991 raising uncertainty about whether it truly informs contemporary practice, and the other allowed inclusion of people already on chronic OCS therapy, to which parenteral therapy would then be added).

Adding continuous low-dose OCS to a patient's asthma management regimen is considered less preferable compared to the other options in this report. The evidence base establishing efficacy is very limited, and the greater concern of the potential adverse effects of chronic systemic corticosteroid therapy (see FAQ 3: What are the side effects?) makes it highly unlikely this treatment will be investigated with further trials. From both a clinical practice perspective and the perspective of major guidelines, there is a clear agreement that use of continuous low-dose oral corticosteroids is an undesirable option that should be reserved for people whose asthma remains uncontrolled despite maximal use of other therapies and assurance that non-pharmacologic measures have also been optimized.

(DynaMed 2018, ERS/ATS 2018, GINA 2018, NVL 2018, Ogirala 1991, ten Brinke 2004)

FAQ 3: What are the side effects?

Comparative evidence

Articles Critically Appraised:*

Certainty	Systematic reviews	Randomized trials	Other article types
High			
Moderate	Farne 2017 (anti-IL-5 therapy)†		
Low	Farne 2017 (anti-IL-5 therapy)‡		
Very low	Kew 2016 (LAMA), Normansell (omalizumab), Farne 2017 (anti-IL-5 therapy)§		
Unusable			
Not used			

*Sources not shown are not relevant for the outcome and/or comparison of interest.
† For outcome adverse events leading to discontinuation for benralizumab
‡ For outcome adverse events leading to discontinuation for mepolizumab and reslizumab
§ For outcome serious adverse events

Quantitative Evidence Review and Evidence Synthesis Synopsis:

The available data for the available therapies do not permit any conclusion about the comparative effect for side effects due to imprecision, inconsistency (for adverse events leading to discontinuation), and Very serious indirectness due to how the outcome of serious adverse events was defined (for instance, serious adverse events likely included hospitalization for asthma exacerbation, which is more appropriately considered an efficacy outcome and could mask actual adverse events). As such, representation of an effect estimate as part of quantitative or qualitative synthesis or expression could be potentially misleading. Therefore, we provide a descriptive summary of adverse events, including less serious and more serious adverse events.

Descriptive summaries

For descriptive summaries of adverse effects associated with the therapeutic regimens, we first describe adverse effects for medium-to-high-intensity ICS + LABA, as this is used as the "cornerstone" baseline therapy for severe asthma and serves as the control group for studies informing this report. Thereafter, we only describe adverse effects for the therapy being considered as an addition to medium-to-high-intensity ICS + LABA, because this is the key question this report addresses (i.e., "What does adding X to ICS + LABA do?"). We consider it unhelpful to repeat the information for medium-to-high-intensity ICS + LABA in each category even though the implicit assumption is the agent in consideration is being added to background ICS + LABA therapy. References are provided at the end of this section rather than after each option given the shared sources used.

Background therapy: Medium-to-high-intensity ICS + LABA

Descriptive summary

Less serious adverse effects may include:

- headache
- dizziness
- upper respiratory symptoms (such as cough or upper respiratory infections like the common cold or a sinus infection)
- bronchitis
- throat irritation
- dysphonia (including a hoarse voice and/or difficulty speaking)
- oropharyngeal candidiasis (a yeast infection in the mouth and/or throat, commonly known as "thrush")
- gastrointestinal symptoms (such as stomach ache, nausea and/or vomiting)
- muscle or back aches, and
- palpitations (possibly due to intermittent premature ventricular contractions).

Of note, patients should be advised to "gargle, swish, and spit" with water after each use of ICS, as this can help reduce the risk of certain side effects, such as oral candidiasis and dysphonia (because it helps ensure that any lingering corticosteroid retained in the oropharyngeal space gets washed/rinsed away).

Serious adverse effects may include:

- heart rate and rhythm problems (such as tachycardia or atrial fibrillation)
- paradoxical bronchospasm
- osteoporosis and/or fracture, and
- serious eye-related adverse effects (such as cataracts or glaucoma).

LAMA (added to medium-to-high-intensity ICS + LABA)

Descriptive summary

Less serious adverse effects may include:

- constipation
- dry mouth
- headache
- urinary tract infection
- fast heart rate or feeling like your heart is fluttering
- bronchitis, and
- upper respiratory symptoms (such as cough, the common cold, sore throat or throat infection, or sinus infection).

Serious adverse effects may include:

- urinary retention
- paradoxical bronchospasm
- angle-closure glaucoma
- hypersensitivity reactions (up to and including anaphylaxis), and
- slowing of the heart.

Anti-IgE therapy (subcutaneous omalizumab) (added to medium-to-high-intensity ICS + LABA)

Descriptive summary

Less serious adverse effects may include:

- injection site reaction
- upper abdominal pain or gastroenteritis
- joint pain
- headache
- fever, and
- upper respiratory symptoms (such as nosebleed and infections like the common cold, a sinus infection, or strep throat).

Serious adverse effects may include hypersensitivity reactions (up to and including anaphylaxis).

Anti-IL-5 therapy (benralizumab, mepolizumab, or reslizumab) (added to medium-to-high-intensity ICS + LABA)

Descriptive summary

Less serious adverse effects may include:

- injection site reaction
- muscle and/or back aches
- headache
- sore throat
- fatigue, and
- fever.

In some cases, people develop antibodies to the medication that can make the medication less effective or ineffective.

Serious adverse effects may include hypersensitivity reactions (up to and including anaphylaxis).

Rarely, mepolizumab has been associated with herpes zoster (reactivation of the varicella-zoster virus), more commonly known as shingles.

Continuous low-dose OCS (added to medium-to-high-intensity ICS + LABA)

Descriptive summary

Adding continuous low-dose OCS to a patient's asthma management regimen is considered less preferable compared to the other options in this report. Although the evidence base establishing efficacy is very limited (see FAQ 2: Will it help my symptoms?), perhaps of greater concern are the potential adverse effects of chronic systemic corticosteroid therapy.

Chronic systemic corticosteroid use has been associated with an increased risk of:

- cataracts
- impaired wound healing, thinning of skin, and easy bruising
- hypertension
- diabetes mellitus
- weight gain
- sodium retention and edema
- immunosuppression, and
- various musculoskeletal effects (such as muscle weakness, osteoporosis, fracture, and tendon rupture, as well as growth suppression if use occurs prior to closure of epiphyseal plates).

Chronic use of systemic corticosteroids can also result in:

- a Cushingoid state and/or Cushing's syndrome (manifested as varying combinations of the effects listed above), and/or
- adrenal suppression (leading to dependence on exogenous corticosteroid intake and requiring a taper if systemic corticosteroids are going to be discontinued).

(DynaMed 2018, DynaMed 2019, ETS/ATS 2014, GINA 2018, NVL 2018)

Evidence report for therapeutic options in severe asthma

Part 2 - Search and Selection

Prepared by EBSCO Information Services

September 4, 2019

Prepared by EBSCO Health Innovations and EBM Development Department:

Brian S. Alper, MD, MSPH, FAAFP, Vice President

Martin Mayer, DMSc, MS, PA-C, Clinical Evidence Synthesizer

Eric Manheimer, PhD, EBM Editor

Methods

First-round searching will consist of searching DynaMed Plus summaries pertinent to the topic. The search starts with DynaMed Plus because DynaMed Plus content is based on a thorough, systematic search and active literature surveillance system.

> Systematic literature surveillance (SLS) has been a cornerstone of creating DynaMed content since its inception. Currently, the SLS team works closely with members of McMaster University's Department of Health Research Methods, Evidence, and Impact to define and refine optimal search strategies, utilizing search terms for methodology and for clinical concepts (especially diagnosis and treatment) for each journal. These filters for PubMed searches are derived from PubMed Clinical Queries, McMaster University Hedges system, and DynaMed search filters and were found to capture >95% of relevant valid articles for use in DynaMed.[1]
> [1]Alper BS, Iorio A. Optimising search filters for active literature surveillance: a concordance study. Global Evidence Summit. Cape Town, South Africa; September 2017.
>
> The SLS team, in collaboration with McMaster University, continually evaluates and improves these filters to keep abreast of the ever-changing medical literature landscape. PubMed searches are performed daily. Each article is assessed by an external screener for clinical relevance, then reviewed by internal staff for both clinical relevance and validity. Any disagreements are settled by the Deputy Editor of the SLS team.
> In addition, the SLS team continually monitors the Journal source list against the list of journals catalogued in MEDLINE and existing DynaMed content to determine the set of journals that provide the highest yield for valid, clinically relevant content. As of November 2018, 507 Journals are systematically searched (see http://dynamed.com/home/content/content-sources). The journal selection threshold leads to routine adjustments to the number of journals selected.

Second-round searching will involve PubMed/MEDLINE® searches for intervention-specific systematic reviews or guidelines that involve a systematic review that are more recent than those identified in first-round searching.

Third-round searching will involve original study tracing from systematic reviews, guidelines or other relevant sources. This may be done to identify additional evidence sources if the results from the first two rounds of searching are insufficient.

Fourth-round searching will involve searches for original evidence reports. Such searching will be limited to areas considered insufficiently addressed by earlier searches, such as focused concepts published after search dates in systematic reviews.

Additional selective searching, such as tracing citations from articles found or seeking related articles, may be done for additional concepts discovered.

Additional evidence updates may also be added continuously from feedback from any source.

FAQ Summary

Results

First-round searching – DynaMed Plus:

DynaMed Plus subsection	Number of article citations	Number of unique references included
Asthma in Adults and Adolescents topic, Anticholinergic agents section, (September 4, 2019)	15	2 (Kew 2016, Sobieraj 2018)
Biologics for the Treatment of Severe Asthma topic, Omalizumab section, Efficacy of omalizumab subsection	11	1 (Normansell 2014)
Biologics for the Treatment of Severe Asthma topic, Mepolizumab section	11	1 (Farne 2017)
Biologics for the Treatment of Severe Asthma topic, Reslizumab section	10	0*
Biologics for the Treatment of Severe Asthma topic, Benralizumab section	9	0*

* This search also retrieved Farne 2017, which was retrieved in an earlier first-round search.

Second-round searching – searches for intervention-specific systematic reviews:

Database	Search string	Number of search results	Number of references included
Not applicable – First-round searching yielded several systematic reviews and we considered it unlikely that a large number of additional trials had been published for these therapies. Therefore, instead of searching for additional systematic reviews, we ran searches for randomized, controlled trials that were published after the close of the search window for each respective systematic review. These searches are documented in fourth-round searching.			

Third-round searching – study tracing from systematic reviews:

Source	Tracing	Number of search results	Number of references included
Not applicable			

Fourth-round searching – searches for original evidence reports:

Database	Search string	Number of search results	Number of references included
PubMed September 5, 2019	omalizumab[tiab] AND ((moderate[tiab] OR severe[tiab] OR moderate-to-severe[tiab]) AND asthma[tiab]) AND randomized controlled trial[pt] AND ("2013/05/13"[PDAT] : "3000/12/31"[PDAT])	14	0*
PubMed September 5, 2019	(tiotropium[tiab] OR umeclidinium[tiab] OR aclidinium[tiab] OR glycopyrro*[tiab]) AND asthma[tiab] AND randomized controlled trial[pt] AND ("2017/10/28"[PDAT] : "3000/12/31"[PDAT])	10	0
PubMed September 5, 2019	(benralizumab[tiab] OR mepolizumab[tiab] OR reslizumab[tiab]) AND asthma[tiab] AND randomized controlled trial[pt] AND ("2017/02/28"[PDAT] : "3000/12/31"[PDAT])	15	0

* One trial (Garcia 2013, n = 41) retrieved by this search is included in Normansell 2014 (see first-round searching) based on data available from conference presentations. We checked Garcia 2013's full text and found it did not add anything to what is in Normansell 2014 (due to data already being included or due to reported outcomes not matching outcomes of interest).

Fifth-round searching: Additional evidence sources/updates

After our report was finished and submitted to Universitätsklinikum Schleswig-Holstein (UKSH), UKSH provided feedback, including noting a recently-published guideline from the European Respiratory Society and American Thoracic Society (ERS/ATS 2019). ERS/ATS 2019 was published in online-ahead-of-print format on September 26, with a MEDLINE® *EDAT*/*entrez* of September 29, so this would not be expected to show in any of our searches. Additionally, ERS/ATS 2019 appears to offer little additional evidence to what we already present herein for the scoped options. For instance:

- the randomized, controlled trials (hereafter "trials") they considered for the addition of anti-interleukin 5 (anti-IL5) therapy were included by the Farne 2017 Cochrane systematic review apart from a couple of trials focused on the potential corticosteroid-sparing effect of anti-IL5 agents, but this is outside the scope of this report (Farne 2017 also excluded trials with such a focus)
- the trials they considered for the addition of long-acting muscarinic antagonist (LAMA) therapy includes one additional trial, but this was understandably excluded from the systematic reviews we appraised due to the trial only being 8 weeks in duration (a trial of that duration is of insufficient duration to provide meaningful insight in this situation)

However, it did address evidence for other therapeutic options beyond the scope of this evidence report, namely macrolide antibiotics and dupilumab, an anti-IL4Rα agent. Further information on these therapies is available in their guideline.

Search summary:

Number of articles screened and selected

	Screened	Selected*
1st-round (DynaMed Plus)	56	4
2nd-round (Systematic review searches)	Not applicable†	
3rd-round (Study tracing)	Not applicable	
4th-round (Original article searches)	39	0
5th-round (Additional sources/updates)‡	1	1
Total	*96*	*5*

* Number shown is after deduplication

† Instead of searching for additional systematic reviews, we searched for trials published after the close of the search window in each respective systematic review. These searches are documented in 4th-round searching.

‡ After our report was finished and submitted to Universitätsklinikum Schleswig-Holstein (UKSH), UKSH provided feedback, including noting a recently-published guideline from the European Respiratory Society and American Thoracic Society (ERS/ ATS 2019). ERS/ATS 2019 was published in online-ahead-of-print format on September 26, with a MEDLINE® EDAT/*entrez* of September 29, so this would not be expected to show in any of our searches. Nevertheless, we included a brief appraisal of this guideline in Critical Appraisal at the request of UKSH, so it constitutes a 5th-round source and is documented here as such.

	Articles selected for evaluation (Author Year)
Systematic reviews	4 (Farne 2017, Kew 2016, Normansell 2014, Sobieraj 2018)
Randomized, controlled trials	0
Other article types (e.g., observational studies, guidelines)	1 (ERS/ATS 2019)

Evidence report for therapeutic options in severe asthma

Part 3 - Critical Appraisal

Prepared by EBSCO Information Services

September 4, 2019

Prepared by EBSCO Health Innovations and EBM Development Department:

Brian S. Alper, MD, MSPH, FAAFP, Vice President

Martin Mayer, DMSc, MS, PA-C, Clinical Evidence Synthesizer

Eric Manheimer, PhD, EBM Editor

Abbreviations

General abbreviations that may appear in this report

CI – confidence interval
CrI – credible interval
HR – hazard ratio
IRR – incidence rate ratio
MA – meta-analysis
MD – mean difference
NA – not applicable
NR – not reported
OR – odds ratio
RCT – randomized, controlled trial
RR – risk ratio, relative risk
RtR – rate ratio
SMD – standardized mean difference
SR – systematic review
SRMA – systematic review and meta-analysis

Abbreviations specific to this report

ACQ-7 – Asthma Control Questionnaire-7
ACT – Asthma Control Test
AQLQ – Asthma Quality of Life Questionnaire
BTS – British Thoracic Society
ERS/ATS - European Respiratory Society/American Thoracic Society
GINA – Global Initiative for Asthma
ICS – inhaled corticosteroid
LABA – long-acting β_2-agonist
LAMA – long-acting muscarinic antagonist
NVL – Nationale VersorgungsLeitlinien (German National Care Guidelines Program)
OCS – oral corticosteroid
SIGN – Scottish Intercollegiate Guidelines Network

Methods

For each study selected for critical appraisal, we assessed for criteria needed for Level 1 [likely reliable] evidence ratings in DynaMed's Levels of Evidence criteria in which evidence quality is labeled in 1 of 3 levels:

- **(level 1 [likely reliable] evidence)** for studies with clinical outcomes and minimal risk of bias;
- **(level 2 [mid-level] evidence)** for studies with clinical outcomes and significant methodological or statistical limitations; and
- **(level 3 [lacking direct] evidence)** for reports that do not include scientific analysis of clinical outcomes or for study types that do not include comparisons between groups.
-

The specific concepts we critically assessed are fully mapped to cover all the criteria used in GRADE. We summarized key concerns identified that reduce the certainty of evidence in categories used for GRADE methods (i.e., risks of bias, indirectness, imprecision, inconsistency, and other considerations if relevant). In the study-level summaries inconsistency assessment was applied to consistency of within-study results – this applies to consistency across related outcomes for both original studies and for systematic reviews, and also applies to consistency across studies when applied to systematic reviews.

FAQ Summary

FAQ 1: What does the treatment involve?

FAQ 2: Will it help my symptoms?

FAQ 3: What are the side effects?

Results

Characteristics and Results of Critically Appraised Studies/Sources

Below is a template for study summaries. At each major level, the intended content is a high-level statement (e.g., "Systematic review and meta-analysis of randomized controlled trials" for the item "Study design"). If there is a need to indicate additional relevant information, do so with a sub-bullet under the parent item. For instance, if downgrading once for "Risk of bias", one would comment "Serious concern" for the "Risk of bias" domain, and then using sub-bullets under the "Risk of bias" item, one would comment on the limitations that resulted in the serious concern. A template is included below, followed by an example summary.

ERS/ATS 2019

Holguin F, Cardet JC, Chung KF, Diver S, Ferreira DS, Fitzpatrick A, Gaga M, Kellermeyer L, Khurana S, Knight S, McDonald VM, Morgan RL, Ortega VE, Rigau D, Subbarao P, Tonia T, Adcock IM, Bleecker ER, Brightling C, Boulet LP, Cabana M, Castro M, Chanez P, Custovic A, Djukanovic R, Frey U, Frankemolle B, Gibson P, Hamerlijnck D, Jarjour N, Konno S, Shen H, Vitary C, Bush A. Management of Severe Asthma: a European Respiratory Society/American Thoracic Society Guideline. Eur Respir J. 2019 Sep 26. pii: 1900588. doi: 10.1183/13993003.00588-2019. [Epub ahead of print] PubMed

As noted in Part 2 Search and Selection, this guideline was published after we submitted the report to UKSH for review, but we consider it briefly here for completeness. It appears to offer little additional evidence to what we already present herein for the scoped options. For instance:

- the randomized, controlled trials (hereafter "trials") they considered for the addition of anti-interleukin 5 (anti-IL5) therapy were included by the Farne 2017 Cochrane systematic review apart from a couple of trials focused on the potential corticosteroid-sparing effect of anti-IL5 agents, but this is outside the scope of this report (Farne 2017 also excluded trials with such a focus)
- the trials they considered for the addition of long-acting muscarinic antagonist (LAMA) therapy includes one additional trial, but this was understandably excluded from the systematic reviews we appraised due to the trial only being 8 weeks in duration (a trial of that duration is of insufficient duration to provide meaningful insight in this situation)

However, it did address evidence for other therapeutic options beyond the scope of this evidence report, namely macrolide antibiotics and dupilumab, an anti-IL4Rα agent. Further information on these therapies is available in their guideline.

FARNE 2017

Farne HA, Wilson A, Powell C, Bax L, Milan SJ. Anti-IL5 therapies for asthma. Cochrane Database Syst Rev. 2017 Sep 21;9:CD010834. doi: 10.1002/14651858.CD010834.pub3 PubMed

Relevant to FAQ2, FAQ3

- **Study design:** systematic review of randomized trials
- **Population:** adults and children with asthma on current standard of care treatment (ICS with or without second controller such as a LABA)
    - most patients had severe eosinophilic asthma, which was similarly defined across studies but with some differences
- **Intervention:** anti-IL-5 therapy
    - anti-IL-5 therapies evaluated were benralizumab in 5 trials, mepolizumab in 4 trials, and reslizumab in 4 trials

- **Comparison:** placebo

- **Study inclusion criteria:** treatment duration ≥ 16 weeks

- **Number of studies:** 4
    - we limited consideration to trials evaluating benralizumab for all outcomes of interest aside from adverse events leading to discontinuation (see "Other considerations")
        - 5 trials evaluated benralizumab but 1 (NCT01947946 2013, n = 13) was terminated early due to sponsor decision and contributed no data
        - See "Other considerations" for number of studies and participants for the outcome of discontinuation due to adverse events for other anti-IL-5 therapies
    - 13 trials in systematic review overall
- **Number of participants:** 2,648
    - 2,648 patients (from 4 trials) were included in the largest meta-analysis for benralizumab (serious adverse events)
        - Sample size listed in the above manner because their reporting of sample size was somewhat unclear (they report a total number of participants in the benralizumab trials, but they then note they only included data for doses of benralizumab that are consistent with clinical use without providing an indication of the final number of participants providing "usable" data)
    - 6,000 patients in all trials in systematic review
        - See "Other considerations" for number of studies and participants for the outcome of discontinuation due to adverse events for other anti-IL-5 therapies
- **Duration of follow-up:** 48 to 56 weeks
    - to be included, treatment period had to be ≥ 16 weeks, but trials of interest all had follow-up durations within the range shown above

- **Results and Certainty:**

Effects of benralizumab (subcutaneous) versus placebo in patients with asthma on exacerbations requiring systemic corticosteroids, asthma control, asthma-related quality of life, serious adverse events, and adverse events leading to discontinuation

Outcome	No of patients (studies)	Effect measure	Effect size (95% CI)	LABA + ICS + benralizumab (subQ) group event rate (%)	LABA + ICS alone group event rate (%)	Both groups combined event rate (%)	Certainty (reason for downgrade)
exacerbations requiring systemic corticosteroids (number per patient)	2,456 (3)	rate ratio	0.62 (95% CI 0.55 to 0.70)	not applicable	not applicable	not applicable	High
asthma control (ACQ-7 continuous; 7-point scale from 0 to 6, with lower scores being better)*	2,359 (3)	mean difference	-0.20 (95% CI -0.29 to -0.11)	not applicable	not applicable	not applicable	High
asthma-related quality of life (AQLQ continuous; 7-point scale from 1 to 7, with lower scores being worse)*	1,541 (3)	mean difference	0.23 (95% CI 0.11 to 0.35)	not applicable	not applicable	not applicable	High
serious adverse events†	2,648 (4)	risk ratio	0.81 (95% CI 0.66 to 1.01)	11.45% (186/1,624)	13.48% (138/1,024)	12.24% (324/2,648)	Very low (imprecision, indirectness [Very serious concern])

adverse events leading to discontinuation	2,597 (3)	risk ratio	2.15 (95% CI 1.02 to 4.57)	1.94% (95% CI 0.92% to 4.12%), as estimated from the control group risk and the risk ratio	0.90% (9/998)	not applicable	Moderate (imprecision)

subQ, subcutaneous

* A change of ≥ 0.5 was reported to be considered the minimum clinically significant difference for both the ACQ-7 and AQLQ scores.

† Serious adverse events were not defined, but the Cochrane review authors noted in their discussion of the results for some of the anti-IL-5 therapies that an asthma exacerbation requiring hospitalization would qualify as a serious adverse event. An asthma exacerbation requiring hospitalization would be better handled as an efficacy outcome, and its inclusion as a "serious adverse event" could mask harms from the therapy. Accordingly, the Cochrane review authors also call for these outcomes to be teased out more appropriately in future trials. Given the nature of the data as they are, we have Very serious concern about the applicability of this outcome, and therefore assigned two downgrades for indirectness. See also comparable comments regarding the outcome of serious adverse events in the Normansell 2014 and Kew 2016 summaries.

- **Other considerations**
  - Restriction of consideration to benralizumab for all outcomes of interest other than adverse events leading to discontinuation:
    - We specified intent to compare add-on therapies to combination ICS + LABA therapy, and all trials investigating benralizumab had background therapy consisting of combination ICS + LABA therapy (with the comparison being benralizumab versus placebo)
    - The other two anti-IL-5 medications (reslizumab and mepolizumab) had trials with background therapy consisting of either ICS only or ICS "+ additional controller" (which may or may not have included LABA); none of the trials clearly had all patients on ICS + LABA.
    - Trials of benralizumab constituted the largest dataset of any of the 3 therapies.
    - Examination of effect sizes across the anti-IL-5 medications revealed a global pattern of consistency in effect size, even more so after accounting for the fact that benralizumab was the only intervention where the trials clearly had ICS + LABA as background therapy (the background therapy for mepolizumab and reslizumab was either ICS alone or ICS "+ additional controller" therapy that may or may not have included a LABA):

Medication	Exacerbation requiring corticosteroids (rate ratio [95% CI])	Health-related quality of life (ACQ-7) (mean difference)	Health-related quality of life (SGRQ) (mean difference)	Serious adverse events (risk ratio [95% CI])	Adverse events leading to discontinuation (risk ratio [95% CI])
mepolizumab subQ	0.45 (95% CI 0.36 to 0.55)	-0.42 (95% CI -0.56 to -0.28)	-7.40 (95% CI -9.50 to -5.29)	0.63 (95% CI 0.41 to 0.97)	0.45 (95% CI 0.11 to 1.80)
mepolizumab IV	0.53 (95% CI 0.44 to 0.64)	-0.11 (95% CI -0.32 to 0.09)	-6.4 (95% CI -9.65 to -3.15)	0.59 (95% CI 0.37 to 0.94)	0.72 (95% CI 0.18 to 2.92)
reslizumab IV	0.43 (95% CI 0.33 to 0.55)	-0.25 (95% CI -0.33 to -0.17)	NR	0.79 (95% CI 0.56 to 1.12)	0.66 (95% CI 0.43 to 1.02)
benralizumab subQ	0.62 (95% CI 0.55 to 0.70)	-0.20 (95% CI -0.29 to -0.11)	NR	0.81 (95% CI 0.66 to 1.01)	2.15 (95% CI 1.02 to 4.57)

ACQ-7, Asthma Control Questionnaire; IV, intravenous; NR, not reported; SGRQ, St. George's Respiratory Questionnaire; subQ, subcutaneous

- The one possible exception to the global pattern of consistency is the outcome of adverse events leading to discontinuation, where the other therapies all had serious or very serious imprecision. The effect estimate for mepolizumab subcutaneous is based on 2 trials totaling 936 patients, mepolizumab intravenous is based on 3 trials totaling 751 patients, and reslizumab intravenous is based on 3 trials totaling 1,160 patients. These analyses provide Low certainty evidence due to imprecision and indirectness (given the issues with background therapy stated above). Reslizumab's confidence interval is mostly on the side of benefit favoring reslizumab, but this is an implausible finding. At most, these therapies may be very tolerable and thus be no different from placebo, but any suggestion of a *reduction* in discontinuation rates is entirely implausible and is more suggestive of poor handling of the outcome of discontinuation due to adverse events than it is a genuine reduction in the risk of this outcome.

KEW 2016
Kew KM, Dahri K. Long-acting muscarinic antagonists (LAMA) added to combination long-acting beta2-agonists and inhaled corticosteroids (LABA/ICS) versus LABA/ICS for adults with asthma. Cochrane Database Syst Rev. 2016 Jan 21;(1):CD011721. PubMed

Relevant to FAQ2, FAQ3

- **Study design:** systematic review of randomized trials
- **Population:** adults whose asthma is not well controlled by combination long-acting beta 2-agonists and inhaled corticosteroids (LABA + ICS)
    - patients in included trials had severe asthma, with mean forced expiratory volume in one second (FEV_1) of about 55% of their predicted value
- **Intervention:** LAMA as add-on to combination LABA + ICS
    - all 3 eligible trials evaluated tiotropium bromide as the LAMA and compared it vs. placebo
- **Comparison:** placebo as add-on to combination LABA + ICS

- **Study inclusion criteria:** duration of at least 12 weeks

- **Number of studies:** 2
    - 3 trials evaluated tiotropium bromide (mostly 5 µg once daily via Respimat)
        - we excluded from consideration 1 of these 3 (Ohta 2014)
            - required only 12-week history of symptomatic asthma
            - only 56% of included patients were taking a LABA at baseline (trial had requirement for baseline ICS but not baseline LABA)
                - Cochrane authors noted that because "baseline data showed that 56.8 percent were taking a LABA" the trial did not meet their inclusion criteria but they decided to include it and assess impact of inclusion with sensitivity analysis and apply a GRADE downgrade for indirectness; it was not included in the Sobieraj 2018 JAMA systematic review ICS + LABA + LAMA vs. ICS + LABA comparison and we also did not include it in this Evidence Report
    - 1 trial was designed to evaluate glycopyrronium bromide, but was withdrawn prior to enrollment
- **Number of participants:** 912
    - 912 in the 2 trials we considered
    - 1,197 total
- **Duration of follow-up:** 48 to 52 weeks

- **Results and Certainty:**

Effects of LABA + ICS + LAMA (tiotropium bromide) vs. LABA + ICS alone on exacerbations, asthma control, asthma-related quality of life, and serious adverse events

Outcome	No of patients (studies)	Effect measure	Effect size (95% CI)	LABA + ICS + LAMA (tiotropium bromide) group event rate (%)	LABA + ICS group alone event rate (%)	Certainty (reason for downgrade)
Exacerbations requiring oral corticosteroids-related outcomes						
exacerbations requiring oral corticosteroids (patients with ≥ 1 exacerbation)	907 (2)	odds ratio	0.76 (95% CI 0.57 to 1.02)	26.93% (122/453)	32.82% (149/454)	Moderate (imprecision)
exacerbations requiring oral corticosteroids (number per patient)	907 (2)	rate ratio	0.79 (95% CI 0.53 to 1.17)	not applicable	not applicable	Very low (inconsistency, such imprecision that one cannot suggest effect or no important effect as more likely)
asthma control (ACQ-7 responders) * †	907 (2)	odds ratio	1.68 (95% CI 1.29 to 2.19)	58.06% (263/453)	45.15% (205/454)	Moderate (inconsistency[1])
asthma control (ACQ-7 continuous; 7-point scale from 0 to 6, with lower scores being better)	907 (2)	mean difference	-0.13 (95% CI -0.23 to -0.02)	not applicable	not applicable	High
asthma-related quality of life (continuous) (AQLQ 7-point scale from 1 to 7; lower scores are worse)	907 (2)	mean difference	0.09 (95% CI -0.03 to 0.20)	not applicable	not applicable	High
serious adverse events†	912 (2)	risk ratio	0.93 (95% CI 0.61 to 1.43)	8.11% (37/456)‡	8.77% (40/456)‡	Very low (imprecision, indirectness [Very serious concern][2])

* Kerstjens 2012a and Kerstjens 2012b were pooled and entered as one row in forest plot (Analysis 1.10) for responder analysis because data were not available for each trial separately. Only these estimates pooled from Kerstjens 2012a and Kerstjens 2012b were extracted for this table because the Analysis 1.10 also included Ohta 2014 which we did not consider eligible. A responder was defined as someone with an improvement of at least 0.5 points in their ACQ-7 score (a 7-point scale from 0 to 6, with lower scores being better).

† The serious adverse events analysis (Analysis 1.5) reported odds ratios based on pooling data from the following 3 trials: Kerstjens 2012a, Kerstjens 2012b, and Ohta 2014. As described above, we considered Ohta 2014 to not our eligibility criteria so we recalculated the pooled effect measure (as risk ratio) including only Kerstjens 2012a and Kerstjens 2012b and report our recalculated results in this table.

‡ Consistent risk in both groups in each of two trials
1 Because results were only presented for the two trials pooled together, we are unable to assess consistency and therefore assigned a downgrade in the domain of inconsistency.
2 The outcome of serious adverse events was not defined, and we have Very serious concerns about the applicability of this outcome given the nature of the evidence for "serious adverse events" in the literature reviewed in this report (see related comments in summaries for Farne 2017 and Normansell 2014).

Other considerations:

- Outcomes not advanced to Part 4 and explanation:
    - Exacerbations requiring oral corticosteroids outcome (patients with > 1) (Analysis 1.1) was not advanced to Part 4 because the Sobieraj 2018 JAMA systematic review included an analysis of this outcome (Fig 2A, Table 3) with identical data for Kerstjens 2012a and Kerstjens 2012b and with the addition of a newer trial (Hamelmann 2017).
    - Asthma control responders outcome (Analysis 1.10) was not advanced to Part 4 because the Sobieraj 2018 JAMA systematic review included identical data for Kerstjens 2012a and Kerstjens 2012b for this outcome (the Cochrane and JAMA analysis both only reported outcome data for each group pooled across both Kerstjens 2012 trials) and additionally included a newer trial (Hamelmann 2017). Furthermore, the Cochrane analysis pooled the Kerstjens 2012 trial data with the Ohta 2014 trial which we decided to exclude (Ohta 2014). The two trials in the Sobieraj 2018 JAMA systematic review had inconsistent findings on this outcome: Kerstjens 2012 trial significantly favored adjuvant tiotropium whereas Hamelmann 2017 showed no significant (or clinically important) difference. Therefore, we conclude on inconsistent evidence for this outcome. Had Ohta 2014 been included, our overall conclusion on inconsistent evidence would not change, because Ohta 2014 had similar results to Hamelmann 2017, also showing no significant difference between groups.
    - Asthma control continuous score analysis outcome (Analysis 1.9) was not advanced to Part 4 because the Sobieraj 2018 JAMA systematic review included identical data for Kerstjens 2012a and Kerstjens 2012b for this outcome and additionally included a newer trial (Hamelmann 2017). Therefore, the pooled estimate from the Cochrane review does not include all the relevant, up-to-date evidence.

NORMANSELL 2014
Normansell R, Walker S, Milan SJ, Walters EH, Nair P. Omalizumab for asthma in adults and children. Cochrane Database Syst Rev. 2014 Jan 13;(1):CD003559. PubMed

Relevant to FAQ2, FAQ3

- **Study design:** systematic review of randomized trials
- **Population:** patients with severe asthma
    - review specified eligibility only as patients with chronic asthma; however, subgroup analyses were performed on basis of severity
    - we included only subgroup of trials that reported on patients with severe asthma, which was defined as step four and above in stepwise guide to asthma management recommended in BTS 2005 and BTS/SIGN 2012 guidelines
    - requirement for LABA at baseline was variable across 6 trials in patients with severe asthma contributing to relevant meta-analyses
        - 4 restricted to patients taking both high-dose ICS and LABA at baseline (Chanez 2010, Hanania 2011, INNOVATE, NCT01007149)
        - 1 restricted to patients taking high-dose ICS plus oral corticosteroids at baseline to maintain asthma control and were classified as most severe; this trial did not require LABA (or another adjuvant to ICS plus oral corticosteroids) at baseline although about 45% were reported to be on LABA at baseline (49% in treatment group and 43% in placebo group) (Holgate 2004a)
        - 1 restricted to patients on ≥ step 4 of NHLBI maintenance treatment (which specifies ICS + LABA or leukotriene receptor antagonist or theophylline or zileuton); the proportion of patients taking LABA was not reported (Bardelas 2012)
- **Intervention:** subcutaneous omalizumab
    - review also reported results with inhaled and IV modes of administration, but we restriction to subcutaneous, as this matches clinical use (inhaled and IV are not used)
- **Comparison:** placebo

- **Study inclusion criteria:** no additional relevant

- **Number of studies:** 7
    - 25 studies included in review overall
    - 7 studies in patients with severe asthma were included and up to 6 of these were included in meta-analyses on our outcomes (with 6 included in the serious adverse events meta-analysis [all except Garcia 2012])
- **Number of participants:** 1,921
    - 6,382 in review overall with up to 1,921 patients with severe asthma included in meta-analyses on extracted outcomes (with 1,921 patients included in the serious adverse events meta-analysis [patients from all trials except Garcia 2012])
- **Duration of follow-up:** 16 to 54 weeks
    - duration ranged from 8 to 60 weeks across all trials in review, and from 16 to 54 weeks in 6 trials in severe patients included in relevant meta-analyses

- **Results and Certainty:**

Effects of LABA + ICS + omalizumab vs. LABA + ICS alone on exacerbations requiring oral steroids, asthma-related quality of life, and serious adverse events in patients with severe asthma

Outcome	No of patients (studies)	Effect measure	Effect size (95% CI)	LABA + ICS + omalizumab group event rate (%)	LABA + ICS group alone event rate (%)	Certainty (reason for downgrade)
exacerbations requiring oral steroids (number per patient)	314* (1; Hanania 2011)	rate ratio	0.66 (95% CI 0.45 to 0.97)	not applicable	not applicable	Moderate (imprecision[1])
quality of life - change from baseline in AQLQ scores (AQLQ 7-point scale from 1 to 7; lower scores are worse)	246 (1; Holgate 2004a)	mean difference	0.26 (95% CI 0.05 to 0.47)	not applicable	not applicable	Moderate (indirectness[2])
serious adverse events†	1,921 (6; Bardelas 2012, Chanez 2010, Hanania 2011, Holgate 2004a, INNOVATE, and NCT01007149)	odds ratio	0.77 (95% CI 0.56 to 1.05)	7.70% (75/974)	9.82% (93/947)	Very low (indirectness [Very serious concern][3], imprecision)

* Analysis 1.2.2 does not report number analyzed in single trial included in plot for this outcome (Hanania 2011); Characteristics of Included Studies table suggests that 848 patients "completed" the trial and 850 were randomized. Consultation of the full text of Hanania 2011 revealed they conducted a trial of adding omalizumab to background asthma therapy comprised of at least high-dose ICS and LABA. They used a stratified randomization mechanism, and background asthma therapy was part of the stratified randomization, specifically whether the patient was taking ICS + LABA alone, ICS + LABA + one other controller therapy that was not oral corticosteroids, or ICS + LABA + oral corticosteroids. The group taking ICS + LABA alone constituted 37% of the patient sample, so with 848 patients providing data for the analysis of the rate ratio, 314 were taking ICS + LABA alone as background therapy.

† The comparison suggested a (nonsignificant) decrease in serious adverse events with omalizumab in the subgroup of trials of patients with severe asthma and in the overall analysis that also included the subgroup of trials of patients with moderate to severe asthma the overall pooled OR showed a statistically significant decrease. It was not clear why the add-on of omalizumab would decrease risk of serious adverse events. This Cochrane review did not explain this nor even provide a definition of serious adverse events. However, the Cochrane review of anti-IL-5 therapies (Farne 2017) suggested that this might be explained if asthma-related adverse events such as exacerbations requiring hospitalization were also classified as "serious adverse events". Farne 2017 also commented that a decrease in serious adverse events attributable to a decrease in asthma-related serious adverse events has the potential to mask a relatively smaller increase in non-asthma-related serious adverse events. For this reason, they recommended that future trials report asthma-related serious adverse events and non-asthma-related serious adverse events as separate outcomes. Indeed, because of the implausible finding of a decrease in serious adverse events in the additional medication arm in some studies we reviewed for our protocol, we specifically noted in our scoping document that "If evidence reports a lower rate of adverse events with add-on therapy, this will not be considered a marker of fewer side effects,

but rather, a marker of poor design or reporting of the outcome of "side effects" or "adverse events" due to the medication use."

[1] We did not assign a downgrade for risk of bias despite this being a subgroup of the patients in Hanania 2011, because Hanania 2011 used stratified randomization (see first footnote for this table). However, we did assign a downgrade for imprecision given the upper bound of the confidence interval for the rate ratio is 0.97, which is compatible with clinically-negligible effects. For instance, even if a patient were having 6 exacerbations requiring corticosteroids every 6 months, the rate ratio of 0.97 means omalizumab may only bring this down to 5.82 exacerbations requiring corticosteroids every 6 months.

[2] In Holgate 2004a trial analyzed for this outcome, only about 45% of included patients were reported to be on LABA at baseline.

[3] Because the Cochrane authors did not define "serious adverse events", it is not clear which specific risks are included, and whether they are primarily asthma-related risks such as such as exacerbations requiring hospitalization (which, if so, could potentially explain a decrease with the addition of omalizumab). Additionally, 2 of the 6 trials included in the meta-analysis did not require LABA at baseline in all patients (Holgate 2004a, Bardelas 2012 – see "Population:" bullet above for details).

Other considerations:

- The Cochrane review also reported a "Symptom score" outcome in subgroup of trials of patients with severe asthma, but it was not further defined in the Cochrane review. Because we were not clear what this outcome represented or how it was assessed in the included trials, we have not included this outcome in the table above. For each of the 4 trials included in the Analysis 1.10.2 forest plot, we reviewed their Characteristics of Included Studies table to learn more about the asthma control-related outcome they reported. Each reported use of a different instrument (ie, Bardelas 2012 - "ACT"; Hanania 2011 - "subscale of AQLQ"; Holgate 2004a - "QoL" [without further elaboration]; and NCT01007149 - "shortened version of the Asthma Control Questionnaire"). If each used a different instrument to measure asthma control, it is not clear that it is appropriate to present the data in the same forest plot when using the mean difference effect measure (as reported in Analysis 1.10.2). Furthermore, we are unable to interpret the mean differences reported for each trial and whether they are clinically important because the scale and its range is not reported. Although the 4 trials were not pooled, two showed a significant benefit of omalizumab (with one having a confidence interval that includes no difference) and two showed no significant difference. In the two that showed a significant benefit, the mean differences were -0.25 (95% CI -0.50 to 0.00) (Hanania 2011) and -0.40 (95% CI -0.75 to -0.05) (Holgate 2004a). Whether one assumes a 5-, 7-, or 10-point scale, such differences are of questionable clinical importance, and the confidence intervals include the possibility of clearly-irrelevant differences.

SOBIERAJ 2018

Sobieraj DM, Baker WL, Nguyen E, Weeda ER, Coleman CI, White CM, Lazarus SC, Blake KV, Lang JE. Association of Inhaled Corticosteroids and Long-Acting Muscarinic Antagonists With Asthma Control in Patients With Uncontrolled, Persistent Asthma: A Systematic Review and Meta-analysis. JAMA. 2018 Apr 10;319(14):1473-1484. PubMed

Relevant to FAQ2, FAQ3

- **Study design:** systematic review of randomized trials
  - observational studies were also specified as eligible, but none met inclusion criteria
- **Population:** patients aged ≥ 12 years old with uncontrolled and persistent asthma
- **Intervention:** LAMA as add-on therapy to combination LABA + ICS
  - all 3 trials that addressed our comparison of interest evaluated tiotropium as the LAMA and compared it vs. placebo
  - review also addressed comparison not relevant to our review of LAMA vs. placebo or another controller as add-on therapy to inhaled corticosteroids
- **Comparison:** placebo as add-on to combination LABA + ICS

- **Study inclusion criteria:** no additional relevant

- **Number of studies:** 3
  - the 3 trials relevant to our review compared tiotropium vs. placebo
  - 15 trials total included in review but 12 addressed comparison not relevant to our review
- **Number of participants:** 1,304
- **Duration of follow-up:** 12 to 48 weeks
  - 48 weeks in 2 trials with 912 patients (the Kerstjens 2012 trials)
  - 12 weeks in 1 trial with 392 patients (Hamelmann 2017)

- **Results and Certainty:**

Effects of LABA + ICS + tiotropium bromide vs. LABA + ICS alone in patients with severe asthma on exacerbations, asthma control, and asthma-related quality of life

Outcome	No of patients (studies)	Effect measure	Effect size (95% CI)	LABA + ICS + tiotropium bromide group event rate (%)	LABA + ICS group alone event rate (%)	Certainty (reason for downgrade)
exacerbations requiring oral corticosteroids (patients with ≥ 1)*	1,299 (3)	risk ratio	0.84 (95% CI 0.57 to 1.22)	26.93% (122/453)	32.82% (149/454)	Very low (such imprecision that one cannot suggest effect or no important effect as more likely)
asthma control						
ACQ-7 responder	1,299 (3)	risk ratio†	• 1.28 (95% CI 1.13 to 1.46) in pooled analysis of 2 trials with 907 patients • 1.01 (95% CI 0.89 to 1.14) in 1 trial with 392 patients	• 58.06% (263/453) in pooled analysis of 2 trials with 907 patients • 73.93% (190/257) in 1 trial with 392 patients	• 45.15% (205/454) in pooled analysis of 2 trials with 907 patients • 73.33% (99/135) in 1 trial with 392 patients	Very low (such inconsistency that one cannot suggest effect or no important effect as more likely)
ACQ-7 score (7-point scale from 0 to 6; lower scores are better)	1,301 (3)	mean difference	-0.07 (95% CI -0.31 to 0.18)	not applicable	not applicable	High
asthma-related quality of life						
AQLQ responder‡	907 (2)	risk ratio	1.11 (95% CI 0.96 to 1.28)	46.80% (212/453)	42.29% (192/454)	Low (imprecision, inconsistency[1])

AQLQ score (7-point scale from 1 to 7; lower scores are worse) §	907 (2)	mean difference	• 0.04 (95% CI −0.13 to 0.20) in 1 trial with 459 patients • 0.14 (95% CI −0.03 to 0.31) in 1 trial with 448 patients	not applicable	not applicable	High

* For calculating group event rates for this outcome, we pooled the data from only the Kerstjens 2012 trials (1 and 2), which both had duration of 48 weeks and which both had similar rates in both groups. We did not include the Hamelmann 2017 trial in these pooled estimates because it had a much shorter duration (only 12 weeks) and therefore, as expected, it had a much lower rate of exacerbations. We plan to conclude on the rate of exacerbations over a period of about one year regardless of group assignment (because there were no differences between groups), and the data pooled from the 2 Kerstjens 2012 trials is most appropriate for informing this conclusion. We did not re-calculate a meta-analytic estimate of the risk ratio excluding Hammelman 2017, as Hammelman 2017 was only weighted at 0.8% in the meta-analysis for this outcome, with the 2 Kerstjens 2012 trials together comprising 99.2% of the weight for the risk ratio estimate.

† Results from pooled results from Kerstjens 2012a and Kerstjens 2012b trials and result from Hamelmann 2017 trial were only reported individually and not pooled.

‡ Data from Kerstjens 2012a and Kerstjens 2012b trials were combined for reporting outcome (and not reported separately).

§ Kerstjens 2012a and Kerstjens 2012b mean differences reported separately only and not combined.

[1] Because these two trials were pooled together without presentation of the estimates from each trial or a measure of heterogeneity, we were unable to sufficiently examine consistency; therefore, we assigned a downgrade for inconsistency

Other considerations:

- Outcomes not advanced to Part 4 and explanation:
    - Asthma quality of life continuous score analysis outcome which included Kerstjens 2012a and Kerstjens 2012b was not advanced to Part 4 because it did not report the pooled results of these two trials. The Kew 2016 Cochrane review also included only Kerstjens 2012a and Kerstjens 2012b for this analysis and reported identical data for each but the Cochrane review also reported their pooled results.
- adverse events not reported so the Cochrane review “serious adverse events” outcome was only relevant adverse event-related outcome relevant to the comparison of ICS + LABA + LAMA vs. ICS + LABA alone

Characteristics of studies identified in Part 2, but not included in Part 3:

Zhang 2018 is an RCT published after the search close date for the Sobieraj 2018 systematic review. It is a 4-armed trial, but only 2 of the arms (with 40 patients in each arm) are relevant for this report: ICS + LABA alone vs. LAMA + ICS + LABA. The trial itself is poorly reported, and the only outcomes of possible interest in this trial are symptom scores assessed via the Asthma Control Test scale and nighttime symptoms scale. The results were reported as mean changes from baseline (± standard deviation). Although no statistical testing was performed to compare the groups of interest, the values reported are clearly similar: 9.50 ± 2.46 vs. 10.12 ± 2.36 for the Asthma Control Test, and 2.40 ± 0.84 vs. 2.38 ± 0.51 for nighttime symptoms. Even if these data were used, they would not impact our overall findings for evidence synthesis, so we judged this trial as not contributing meaningfully to this report and did not prepare a full summary of it.

Evidence report for therapeutic options in severe asthma

Part 4 - Evidence Synthesis

Prepared by EBSCO Information Services

September 10, 2019

Prepared by EBSCO Health Innovations and EBM Development Department:

Brian S. Alper, MD, MSPH, FAAFP, Vice President

Martin Mayer, DMSc, MS, PA-C, Clinical Evidence Synthesizer

Eric Manheimer, PhD, EBM Editor

Abbreviations

General abbreviations that may appear in this report

CI – confidence interval
CrI – credible interval
HR – hazard ratio
IRR – incidence rate ratio
MA – meta-analysis
MD – mean difference
NA – not applicable
NR – not reported
OR – odds ratio
RCT – randomized, controlled trial
RR – risk ratio, relative risk
RtR – rate ratio
SMD – standardized mean difference
SR – systematic review
SRMA – systematic review and meta-analysis

Abbreviations specific to this report

ACQ-7 – Asthma Control Questionnaire-7
ACT – Asthma Control Test
AQLQ – Asthma Quality of Life Questionnaire
BTS – British Thoracic Society
ERS/ATS - European Respiratory Society/American Thoracic Society
GINA – Global Initiative for Asthma
ICS – inhaled corticosteroid
LABA – long-acting β2-agonist
LAMA – long-acting muscarinic antagonist
NVL – Nationale VersorgungsLeitlinien (German National Care Guidelines Program)
OCS – oral corticosteroid
SIGN – Scottish Intercollegiate Guidelines Network

Methods

Where evidence is very limited, or the FAQ is scoped as a descriptive response, such that no evidence synthesis or processing is applied, the descriptive summaries will be placed in Part 5 and not repeated here.

For each FAQ for which evidence synthesis or processing is considered, the key concepts (results and factors affecting certainty of the results) from the included studies that are most relevant to evidence synthesis will be summarized in Evidence Review Tables. For each outcome, Evidence Synthesis Process tables will then articulate the method selected for evidence synthesis and justification of that method. We will do this for the effect estimate (i.e., answering the question “Is there a difference between the intervention and comparator?”) and results will be presented with GRADE-based certainty of evidence ratings related to the certainty of effect estimates. For FAQs which require noncomparative/option-specific responses (i.e., the FAQ is “What will happen with this option?” rather than “How do things change with this option?”) the Evidence Synthesis Process tables will be extended to include the method to produce noncomparative responses.

Results

FAQ 1: What does the treatment involve?

Evidence synthesis does not apply. Please see Part 5 for answers to this FAQ.

FAQ 2: Will it help my symptoms?

Medium-to-high-intensity ICS + LABA + LAMA vs. medium-to-high-intensity ICS + LABA

Evidence Review Table for FAQ2:

Effects of LABA + ICS + LAMA (tiotropium bromide) vs. LABA + ICS alone* (Kew 2016)

Outcome	No of patients (studies)	Effect measure	Effect size (95% CI)	Certainty (reason for downgrade)
exacerbations requiring oral corticosteroids (number per patient)	907 (2)	rate ratio	0.79 (95% CI 0.53 to 1.17)	Very low (inconsistency, such imprecision that one cannot suggest either effect or no important effect as more likely)
AQLQ score (7-point scale from 1 to 7; lower scores are worse)	907 (2)	mean difference	0.09 (95% CI -0.03 to 0.20)†	High

*Additional outcomes reported in Kew 2016 Cochrane review are not included here because Sobieraj 2018 JAMA systematic review provides meta-analyses on these outcome that include more current and relevant data.

† Mean differences were small with narrow CIs in both trials: 0.04 points (95% CI -0.13 to 0.2 points) in Kerstjens 2012a and 0.14 points (95% CI -0.03 to 0.31) in Kerstjens 2012b)

Effects of LABA + ICS + LAMA (tiotropium bromide) vs. LABA + ICS alone (Sobieraj 2018)

Outcome	No of patients (studies)	Effect measure	Effect size (95% CI)	Certainty (reason for downgrade)
exacerbations requiring oral corticosteroids (patients with ≥ 1 exacerbation)	1,299 (3)	risk ratio	0.84 (95% CI 0.57 to 1.22)	Very low (such imprecision that one cannot suggest either effect or no important effect as more likely)
asthma control				
ACQ-7 responder*	1,299 (3)	risk ratio	• 1.28 (95% CI 1.13 to 1.46) in pooled analysis of 2 trials with 907 patients • 1.01 (95% CI 0.89 to 1.14) in 1 trial with 392 patients	Very low (such inconsistency that one cannot suggest either effect or no important effect as more likely)

ACQ-7 score (7-point scale from 0 to 6; lower scores are better)	1,301 (3)	mean difference	-0.07 (95% CI -0.31 to 0.18)	High
asthma-related quality of life				
AQLQ responder†	907 (2)	risk ratio	1.11 (95% CI 0.96 to 1.28)	Low (imprecision, inconsistency)

* Pooled results from Kerstjens 2012a and Kerstjens 2012b trials and result from Hamelmann 2017 trial were only reported individually and not pooled.

† Data from Kerstjens 2012a and Kerstjens 2012b trials were combined for reporting outcome (and not reported separately).

Evidence Synthesis Process for FAQ2:

Outcome	Approach taken and justification: measure of comparative effect	Results: measure of comparative effect
exacerbations requiring oral corticosteroids (number per patient)	**Meta-analysis already done, qualitative expression** The meta-analysis for this outcome in Kew 2016 has serious imprecision with confidence intervals compatible with no effect, important reduction, and possibly important increase. Qualitative expression was selected because any implied difference from point estimate was considered potentially misleading due to the wide confidence intervals.	**Insufficient evidence to estimate comparative effect** Certainty is Very low with downgrades due to inconsistency and such imprecision that one cannot suggest effect or no important effect as more likely.
exacerbations requiring oral corticosteroids (patients with ≥ 1 exacerbation)	**Meta-analysis already done, qualitative expression** The meta-analysis for this outcome in Sobieraj 2018 has serious imprecision with confidence intervals compatible with no effect, important reduction, and possibly important increase. Qualitative expression was selected because any implied difference from point estimate was considered potentially misleading due to the wide confidence intervals.	**Insufficient evidence to estimate comparative effect** Certainty is Very low with downgrades due to inconsistency and such imprecision that one cannot suggest effect or no important effect as more likely.
asthma control/asthma-related quality of life (includes ACQ-7 and AQLQ scores measured by mean differences and responder rates)	**Qualitative synthesis of multiple meta-analyses** Four reported measures of asthma control/asthma-related quality of life are highly inter-related, are meta-analyzed by Kew 2016 (AQLQ score) and Sobieraj 2018 (ACQ-7 score, ACQ-7 responder, and AQLQ responder), and are considered to be expressing the same general outcome. Because the preponderance of data suggests no important effect, qualitative synthesis is selected as easier for patient understanding.	**No important effect** Certainty for the general outcome is Moderate due to inconsistency across specific effect measures and outcomes

We do not have enough evidence to know whether people taking a LAMA in addition to ICS + LABA therapy have a similar, higher, or lower rate of exacerbations requiring corticosteroids compared to people taking ICS + LABA therapy alone. (Very low certainty)

We do not have enough evidence to know whether people taking a LAMA in addition to ICS + LABA therapy have a similar, higher, or lower risk of having one or more exacerbations requiring corticosteroids compared to people taking ICS + LABA therapy alone. (Very low certainty)

There may be little to no difference in overall asthma symptom control or quality of life when taking a LAMA in addition to ICS + LABA therapy compared to taking ICS + LABA alone. (Moderate certainty)

Medium-to-high-intensity ICS + LABA + anti-IgE therapy (subcutaneous omalizumab) vs. medium-to-high-intensity ICS + LABA

Evidence Review Table for FAQ2:

Effects of LABA + ICS + omalizumab (subcutaneous) versus LABA + ICS alone (Normansell 2014)

Outcome	No of patients (studies)	Effect measure	Effect size (95% CI)	Certainty (reason for downgrade)
exacerbations requiring oral steroids (number per patient)	314 (1)*	rate ratio	0.66 (95% CI 0.45 to 0.97)	Moderate (imprecision[1])
quality of life -change from baseline in AQLQ score (AQLQ 7-point scale from 1 to 7; lower scores are worse)	246 (1)	mean difference	0.26 (95% CI 0.05 to 0.47)	Moderate (indirectness[2])

* Hanania 2011 conducted a trial of adding omalizumab to background asthma therapy comprised of at least high-dose ICS and LABA. They used a stratified randomization mechanism, and background asthma therapy was part of the stratified randomization, specifically whether the patient was taking ICS + LABA alone, ICS + LABA + one other controller therapy that was not oral corticosteroids, or ICS + LABA + oral corticosteroids. The group taking ICS + LABA alone constituted 37% of the patient sample, so with 848 patients providing data for the analysis of the rate ratio, 314 were taking ICS + LABA alone as background therapy.

[1] We did not assign a downgrade for risk of bias despite this being a subgroup of the patients in Hanania 2011, because Hanania 2011 used stratified randomization (see above footnote). However, we did assign a downgrade for imprecision given the upper bound of the confidence interval for the rate ratio is 0.97, which is compatible with clinically-negligible effects. For instance, even if a patient were having 6 exacerbations requiring corticosteroids every 6 months, the rate ratio of 0.97 means omalizumab may only bring this down to 5.82 exacerbations requiring corticosteroids every 6 months.

[2] In Holgate 2004a trial analyzed for this outcome, only about 45% of included patients were reported to be on LABA at baseline.

Evidence Synthesis Process for FAQ2:

Outcome	Approach taken and justification: measure of comparative effect	Results: measure of comparative effect
exacerbations requiring oral corticosteroids (number per patient)	**Meta-analysis already done, use confidence interval to express range** Because the confidence interval suggests clearly meaningful differences and differences of questionable importance, we emphasize the confidence interval rather than the point estimate, as using the point estimate could imply greater precision than actually exists.	**Rate ratio 0.66 (95% CI 0.45 to 0.97)** Certainty is Moderate with downgrade due to imprecision.
asthma control/asthma-related quality of life (AQLQ score, measured by mean difference)	**Meta-analysis already done, qualitative expression** Because the evidence amounts to a continuous measure (expressed as mean difference) and suggests no important effect, qualitative expression is selected as easier for patient understanding.	**No important effect** Certainty is Moderate with downgrade due to indirectness because only about 45% of included patients were reported to be on LABA at baseline.

People who take omalizumab in addition to ICS + LABA therapy may have fewer exacerbations requiring steroids compared to people who take ICS + LABA therapy alone. The effect may be very small or it may reduce the number of exacerbations requiring steroids by about one-half. (Moderate certainty)

There may be little to no difference in overall asthma symptom control or quality of life when taking omalizumab in addition to ICS + LABA therapy compared to taking ICS + LABA alone. (Moderate certainty)

Medium-to-high-intensity ICS + LABA + anti-IL-5 therapy vs. medium-to-high-intensity ICS + LABA

Evidence Review Table for FAQ2:

Effects of benralizumab + LABA + ICS (subcutaneous) versus LABA + ICS alone (Farne 2017)*

Outcome	No of patients (studies)	Effect measure	Effect size (95% CI)	Certainty (reason for downgrade)
exacerbations requiring systemic corticosteroids (number per patient)	2,456 (3)	rate ratio	0.62 (95% CI 0.55 to 0.70)	High
asthma control (ACQ-7 continuous; 7-point scale from 0 to 6, with lower scores being better)†	2,359 (3)	mean difference	-0.20 (95% CI -0.29 to -0.11)	High
asthma-related quality of life (AQLQ continuous; 7-point scale from 1 to 7, with lower scores being worse)†	1,541 (3)	mean difference	0.23 (95% CI 0.11 to 0.35)	High

* Effect estimates for the other anti-IL-5 therapies were consistent with the effect estimate for benralizumab subcutaneous, and the trials for benralizumab subcutaneous matched the desired background therapy (LABA + ICS), so we limited consideration to benralizumab subcutaneous

† A change of ≥ 0.5 was reported to be considered the minimum clinically significant difference for both the ACQ-7 and AQLQ scores.

Evidence Synthesis Process for FAQ2:

Outcome	Approach taken and justification: measure of comparative effect	Results: measure of comparative effect
exacerbations requiring oral corticosteroids (number per patient)	**Meta-analysis already done, use confidence interval to express range** Because our evidence synthesis for omalizumab presented the results of the confidence interval, we adopt the same approach here for purposes of seeing the relative comparison.	**Rate ratio 0.62 (95% CI 0.55 to 0.70)** Certainty is High.
asthma control/asthma-related quality of life (includes ACQ-7 and AQLQ scores, both measured by mean differences)	**Qualitative synthesis of multiple meta-analyses** Because the evidence for asthma control/asthma-related quality of life amounts to continuous outcomes (expressed as mean differences) and because each shows High certainty evidence of no important effect, qualitative synthesis of these two highly inter-related outcomes is selected as easier for patient understanding.	**No important effect** Certainty is High.

Compared to people taking ICS + LABA alone, people who take anti-IL-5 therapy in addition to ICS + LABA therapy will likely reduce their number of exacerbations requiring steroids by about one-third to one-half. (High certainty)

There is likely little to no difference in overall asthma symptom control or quality of life when taking anti-IL-5 therapy in addition to ICS + LABA therapy compared to taking ICS + LABA alone. (High certainty)

Medium-to-high-intensity ICS + LABA + continuous low-dose oral corticosteroids (OCS) vs. medium-to-high-intensity ICS + LABA

Descriptive summary

As noted in Part 1 Scoping, evidence is very limited concerning the addition of continuous low-dose oral corticosteroids. For instance, the 2018 GINA guideline only cites the 2014 European Respiratory Society and American Thoracic Society guideline for supporting evidence, which in turn notes OCS therapy is "often added as maintenance therapy in severe asthma". However, it also notes "it is not yet clear whether continuous low-dose OCS are better than multiple discontinuous bursts for controlling exacerbations" and that "optimal timing for initiation of OCS therapy has also not been defined". It then discusses two very small trials (Ogirala 1991, ten Brinke 2004) investigating parenteral corticosteroid therapy (total sample size considering both trials = 34), but in addition to the limitations in sample size, there are also other methodologic limitations (e.g., one of the trials was published in 1991 raising uncertainty about whether it truly informs contemporary practice, and the other allowed inclusion of people already on chronic OCS therapy, to which parenteral therapy would then be added).

Adding continuous low-dose OCS to a patient's asthma management regimen is considered less preferable compared to the other options in this report. The evidence base establishing efficacy is very limited, and the greater concern of the potential adverse effects of chronic systemic corticosteroid therapy (see FAQ 3: What are the side effects?) makes it highly unlikely this treatment will be investigated with further trials.

(DynaMed 2018, ERS/ATS 2018, GINA 2018, NVL 2018, Ogirala 1991, ten Brinke 2004)

FAQ 3: What are the side effects?

Medium-to-high-intensity ICS + LABA + LAMA vs. medium-to-high-intensity ICS + LABA

Evidence Review Table for FAQ3:

Effects of LABA + ICS plus tiotropium bromide vs. LABA + ICS alone (Kew 2016)

Outcome	No of patients (studies)	Effect measure	Effect size (95% CI)	Certainty (reason for downgrade)
serious adverse events*	912 (2)	risk ratio	0.93 (95% CI 0.61 to 1.43)	Very low (imprecision, indirectness [Very serious concern][1])

* The serious adverse events analysis reported odds ratios based on pooling data from the following 3 trials: Kerstjens 2012a, Kerstjens 2012b, and Ohta 2014. As described in the Part 3 summary of Key 2016, we considered Ohta 2014 to not our eligibility criteria so we recalculated the pooled effect measure (as risk ratio) including only Kerstjens 2012a and Kerstjens 2012b and report our recalculated pooled results in this table.

[1] Because Cochrane authors did not define "serious adverse events", it is not clear which specific risks are included, and whether they are primarily asthma-related risks such as exacerbations requiring hospitalization (which, if so, could potentially explain a decrease with the addition of add-on tiotropium bromide). Additional detail is in Part 3.

Evidence Synthesis Process for FAQ3:

Outcome	Approach taken and justification: measure of comparative effect	Results: measure of comparative effect
serious adverse events	**Descriptive summary** The available data for LAMAs do not permit any conclusion about the comparative effect, and as noted above and in Part 3, we have concerns regarding how this outcome was defined. As such, representation of an effect estimate as part of quantitative or qualitative synthesis or expression could be potentially misleading. Therefore, we provide a descriptive summary of adverse events for LAMAs, including less serious and more serious adverse events.	**Not applicable** See Part 5 for descriptive summary of adverse effects.

Medium-to-high-intensity ICS + LABA + anti-IgE therapy (subcutaneous omalizumab) vs. medium-to-high-intensity ICS + LABA

Evidence Review Table for FAQ2:

Effects of LABA + ICS + omalizumab (subcutaneous) vs. LABA + ICS alone (Normansell 2014)

Outcome	No of patients (studies)	Effect measure	Effect size (95% CI)	Certainty (reason for downgrade)
serious adverse events	1,921 (6)	odds ratio	0.77 (95% CI 0.56 to 1.05)	Very low (indirectness [Very serious concern][1], imprecision)

[1] Because the Cochrane authors did not define "serious adverse events", it is not clear which specific risks are included, and whether they are primarily asthma-related risks such as such as exacerbations requiring hospitalization (which, if so, could potentially explain the suggestion of a decrease with the addition of omalizumab). Additionally, 2 of the 6 trials included in the meta-analysis did not require LABA at baseline in all patients. Additional detail is in Part 3.

Evidence Synthesis Process for FAQ2:

Outcome	Approach taken and justification: measure of comparative effect	Results: measure of comparative effect
serious adverse events	**Descriptive summary** The available data for omalizumab fail to reach statistical significance but still suggest a possible reduction in serious adverse events. The notion of omalizumab reducing serious adverse events is entirely implausible and may be partly due to concerns we raise above and in Part 3 regarding how this outcome was defined. As we stated in scoping, any quantitative suggestion of a reduction in adverse events would not be treated as such, but rather, an indicator of poor handling of the outcome. Therefore, we provide a descriptive summary of adverse events for omalizumab, including less serious and more serious adverse events.	**Not applicable** See Part 5 for descriptive summary of adverse effects.

Medium-to-high-intensity ICS + LABA + anti-IL-5 therapy vs. medium-to-high-intensity ICS + LABA

Evidence Review Table for FAQ2:

Effects of benralizumab (subcutaneous) versus placebo (Farne 2017)

Outcome	No of patients (studies)	Effect measure	Effect size (95% CI)	Certainty (reason for downgrade)
serious adverse events*	2,648 (4)	risk ratio	0.81 (95% CI 0.66 to 1.01)	Very low (imprecision, indirectness [Very serious concern][1])
adverse events leading to discontinuation	2,597 (3)	risk ratio	2.15 (95% CI 1.02 to 4.57)	Moderate (imprecision)

* Effect estimates for the other anti-IL-5 therapies were consistent with the effect estimate for benralizumab subcutaneous, and the trials for benralizumab subcutaneous matched the desired background therapy (LABA + ICS), so we limited consideration to benralizumab subcutaneous

[1] Serious adverse events were not defined, but the Cochrane review authors noted in their discussion of the results for some of the anti-IL-5 therapies that an asthma exacerbation requiring hospitalization would qualify as a serious adverse event. An asthma exacerbation requiring hospitalization would be better handled as an efficacy outcome, and its inclusion as a "serious adverse event" could mask harms from the therapy. Given the nature of the data as they are, we have Very serious concern about the applicability of this outcome, and therefore assigned two downgrades for indirectness. Additional detail is in Part 3.

Descriptive Evidence Review for FAQ2:

We focused on benralizumab subcutaneous for all outcomes other than adverse events leading to discontinuation for reasons stated in Part 3. However, we gave additional consideration to the other therapies for the outcome of adverse events leading to discontinuation because their effect estimates were not clearly consistent with the effect estimate for benralizumab subcutaneous. The other therapies all had serious or very serious imprecision for this outcome:

- mepolizumab subcutaneous: RR 0.45 (95% CI 0.11 to 1.80; based on 2 trials totaling 936 patients)
- mepolizumab intravenous: RR 0.72 (95% CI 0.18 to 2.92; based on 3 trials totaling 751 patients)
- reslizumab intravenous: RR 0.66 (95% CI 0.43 to 1.02; based on 3 trials totaling 1,160 patients)

These analyses provide Low certainty evidence due to imprecision and indirectness (due to background therapies being varied, with only benralizumab subcutaneous consistently having trials with background therapy amounting to LABA + ICS). Reslizumab's confidence interval is mostly on the side of benefit favoring reslizumab. However, at most, these therapies may be very tolerable and thus be no different from placebo in terms of tolerability; any suggestion that these therapies might *reduce* discontinuation rates is implausible and suggests poor handling of the outcome of discontinuation due to adverse events more than a genuine reduction in the risk of discontinuation.

Evidence Synthesis Process for FAQ2:

Outcome	Approach taken and justification: measure of comparative effect	Results: measure of comparative effect
serious adverse events	**Descriptive summary** The available data for benralizumab subcutaneous fail to reach statistical significance but still suggest a possible reduction in serious adverse events with anti-IL-5 therapy. Other anti-IL-5 therapies show consistent effects, with some reaching statistical significance. Nevertheless, the notion of anti-IL-5 therapy reducing serious adverse events is entirely implausible and may be partly due to concerns we raise above and in Part 3 regarding how this outcome was defined. As we stated in scoping, any quantitative suggestion of a reduction in adverse events would not be treated as such, but rather, an indicator of poor handling of the outcome. Therefore, we provide a descriptive summary of adverse events for anti-IL-5 therapies, including less serious and more serious adverse events.	**Not applicable** See Part 5 for descriptive summary of adverse effects.
adverse events leading to discontinuation	**Descriptive summary** The data for benralizumab subcutaneous suggest a possible increase in adverse events leading to discontinuation, but the other three anti-IL-5 therapies suggest there may be an increase or there may be no increase in adverse events leading to discontinuation. As such, quantifying results based on benralizumab's results alone could be misleading, and pooling results for all anti-IL-5 therapies would be highly unlikely to offer further insight beyond what can be ascertained from examining the data in their present form. This led us to consider a qualitative approach describing the pattern of the results. However, a qualitative synthesis would amount to a conclusion that anti-IL-5 therapy may be tolerable or may make people want to stop the treatment depending on the person and therapy used. This is essentially an obvious statement for any intervention or intervention class that carries a risk for side effects. Additionally, this outcome is only reported for the anti-IL-5 therapies and not for omalizumab or LAMA, so its usefulness as an outcome is questionable. Therefore, concluding with a qualitative statement is not likely to be helpful for patients or clinicians, and we deemed a descriptive summary of adverse effects most appropriate.	**Not applicable** See Part 5 for descriptive summary of adverse effects.

Evidence report for therapeutic options in severe asthma

Reference list

Prepared by EBSCO Information Services

September 10, 2019

Prepared by EBSCO Health Innovations and EBM Development Department:

Brian S. Alper, MD, MSPH, FAAFP, Vice President

Martin Mayer, DMSc, MS, PA-C, Clinical Evidence Synthesizer

Eric Manheimer, PhD, EBM Editor

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