



Effective Health Care

Azithromycin vs. Biologics in Severe Asthma

Results of Topic Selection Process & Next Steps

The nominator, Kaiser Permanente Care Management Institute, is interested in a new evidence review on comparative effectiveness and safety of long-term azithromycin therapy versus various other biologics (e.g., omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab) for the prevention of exacerbations in patients with severe asthma to develop new guidelines.

Because no original research addresses the nomination, a new review is not feasible at this time. No further activity on this nomination will be undertaken by the Effective Health Care (EHC) Program.

Topic Brief

Topic Name: Azithromycin vs Other Biologics for Severe Asthma

Nomination Date: 11/10/2017

Topic Brief Date: 1/19/2018

Author

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Conflict of Interest: None

Summary

- We found no studies that covered the scope of the nomination. We identified no head-to-head trials comparing the two classes of pharmacologic agents i.e. macrolides to biologic agents anti IgE or anti-interleukins.
- Three completed and one in-process Cochrane reviews of placebo controlled trials were identified. While these do not directly address the comparison of interest to the nominator, these may be useful.
 - One review of 23 studies (10 trials of azithromycin) compared the effectiveness of macrolides to placebo for the management of chronic asthma. Overall, low quality evidence suggested no significant benefit for most primary outcomes.
 - A second review of 25 studies compared omalizumab to placebo as an adjunct to inhaled corticosteroids in patients with moderate to severe asthma and reported benefit from it.
 - Findings from a third placebo controlled review of 13 studies (4 mepolizumab, 4 reslizumab, 5 benralizumab) supports the use of anti-IL-5 treatments as an adjunct to standard of care in people with severe eosinophilic asthma and poor control.
 - There is an in process Cochrane review (protocol posted on Jan 22, 2018) that includes all biologic agents entitled: Anti-interleukin-13 and anti-

interleukin-4 agents versus placebo, anti-interleukin-5 or anti-immunoglobulin-E agents, for children and adults with asthma

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Background

Asthma is a chronic inflammatory disorder of the airways, characterized by varying degrees of airflow obstruction. Bronchoconstriction, inflammatory cell infiltration, and airway edema reduce airflow intermittently, often in response to specific exposures, resulting in respiratory symptoms.¹ In the United States (US), the current prevalence of asthma has increased over the past decade, from an estimated 22.2 million Americans in 2005 to 24.0 million Americans in 2014.^{3,4} Asthma can significantly impact patients' and families' quality-of-life and ability to pursue activities such as school, work, and exercise. Globally, asthma ranks 14th based on the burden of disease, as measured by disability adjusted life years.⁵ In the US, asthma contributes significantly to healthcare resource utilization and associated costs. The majority of patients with asthma report an exacerbation in the past year, with more than one-fourth of adults requiring consequent urgent medical care. For example, in 2012, asthma was one of the top twenty leading diagnosis groups for primary care visits and was the main reason for 1.8 million emergency department visits and 439,000 hospitalizations. While the severity of disease varies between patients and over time in the same patient, asthma can be fatal, accounting for approximately 1 death per 100,000 Americans.⁶

Most clinical practice guidelines recommend a stepwise approach to pharmacological therapy to control asthma with patients at the severe end of the spectrum receiving a combination of long acting inhaled beta-2 agonists and high dose inhaled and oral corticosteroids.⁷

Macrolides (including azithromycin) are a class of antibiotics that are widely used in the treatment of various infectious diseases, including respiratory tract infections. The anti-inflammatory effect of this class of antibiotics, appears to decrease bronchial hyperresponsiveness associated with eosinophilic inflammation.⁸ Macrolides have been shown to be effective in the long-term treatment of cystic fibrosis, diffuse panbronchiolitis and chronic obstructive pulmonary disease, and are not associated with an increased risk of adverse events.^{9, 10} Since bacterial infections are more common and more severe in patients with asthma, and viruses are thought to increase susceptibility to bacterial infection, leading to increasing asthma exacerbation risk, macrolides have been recently become the subject of research for this condition.¹¹

The recent development of new biologic agents have offered new hope to patients with poor asthma control. The FDA has approved a number of biologic agents for the treatment for severe persistent allergic asthma that is inadequately controlled by inhaled corticosteroids (ICS) in adults and adolescents (aged ≥ 12 years). These include omalizumab, an anti-IgE antibody for the treatment of moderate to severe asthma and anti-interleukins (mepolizumab, reslizumab, benralizumab, dupilumab) for severe asthma in patients with eosinophilic phenotype.¹²

Therefore, there is great interest in the evidence base related to the comparative effectiveness of macrolides versus biologic agents.

The key questions for this nomination are:

1. What is the comparative effectiveness and safety of long-term azithromycin therapy versus various other biologics (e.g., omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab) for the prevention of asthma exacerbations in patients with severe asthma?

To define the inclusion criteria for the key questions we specify the population, interventions, comparators, outcomes (PICO) of interest (Table 1).

Table 1. Key Questions and PICOTS

Key Questions	What is the comparative effectiveness and safety of long-term azithromycin therapy versus various other biologics (e.g., omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab) for the prevention of asthma exacerbations in patients with severe asthma?
Population	Adults, adolescents, children with severe asthma
Interventions	Azithromycin/macrolides
Comparators	omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab
Outcomes	Exacerbations, Quality of life, Antibiotic resistance, adverse events, short term and long term side effects.

Methods

We assessed nomination Azithromycin vs. Biologics in Severe Asthma, for priority for a systematic review or other AHRQ EHC report with a hierarchical process using established selection criteria (Appendix A). Assessment of each criteria determined the need for evaluation of the next one.

1. Determine the *appropriateness* of the nominated topic for inclusion in the EHC program.
2. Establish the overall *importance* of a potential topic as representing a health or healthcare issue in the United States.
3. Determine the *desirability of new evidence review* by examining whether a new systematic review or other AHRQ product would be duplicative.
4. Assess the *potential impact* a new systematic review or other AHRQ product.
5. Assess whether the *current state of the evidence* allows for a systematic review or other AHRQ product (feasibility).
6. Determine the *potential value* of a new systematic review or other AHRQ product.

Appropriateness and Importance

We assessed the nomination for appropriateness and importance.

Desirability of New Review/Duplication

We searched for high-quality, completed or in-process evidence reviews published in the last five years on the key questions of the nomination and found no appropriate head to head trials. See Appendix B for sources searched.

Impact of a New Evidence Review

The impact of a new evidence review was qualitatively assessed by analyzing the current standard of care, the existence of potential knowledge gaps, and practice variation. We considered whether it was possible for this review to influence the current state of practice through various dissemination pathways (practice recommendation, clinical guidelines, etc.).

Feasibility of New Evidence Review

We conducted a literature search in PubMed and PsycInfo from January 2013 to January 2018.

We conducted a separate search on Pubmed for heads-to-head trial comparing macrolides such as azithromycin with biologic agents for treatment of severe asthma.

See Appendix C for the PubMed search strategy.

Compilation of Findings

We constructed a table with the selection criteria and our assessments (Appendix A).

Results

Appropriateness and Importance

This is an appropriate and important topic.

Desirability of a new Review/Duplication

We did not identify reviews that assessed the comparison of interest to the nominator. However we identified three reviews of placebo controlled trials which we mention as they might be useful to the nominator.

We retrieved two fairly recent Cochrane reviews on the topic, one addressing macrolides, including azithromycin (literature search date through April 2015).¹³ The review of 23 studies (10 trials of azithromycin) compared the effectiveness of macrolides to placebo for the management of chronic asthma. Overall, low quality evidence suggested no significant benefit for most primary outcomes. The other addressing omalizumab (literature search date through 2013).¹⁴ Twenty five- studies compared omalizumab to placebo as an adjunct to inhaled corticosteroids in patients with moderate to severe asthma and reported benefit, although with some uncertainty about which sub type of asthma patients would benefit most.

Findings from a third placebo controlled review of 13 studies (4 mepolizumab, 4 relizumab, 5 benralizumab) supports the use of anti-IL-5 treatments as an adjunct to standard of care in people with severe eosinophilic asthma and poor control.¹⁵

There is a Cochrane protocol posted on Jan 22, 2018 for review that includes all biologic agents entitled Anti-interleukin-13 and anti-interleukin-4 agents versus placebo, anti-interleukin-5 or anti-immunoglobulin-E agents, for children and adults with asthma.¹⁶

Impact

A new evidence review examining Azithromycin versus Biologic agents for prevention of asthma exacerbation would have a high impact. Existing clinical guidelines do not address which patients would best benefit from azithromycin versus the newer biologics, and a new review would potentially close this knowledge gap.

Feasibility of a New Evidence Review

A new evidence review examining Azithromycin versus Biologic agents for prevention of asthma exacerbation is not feasible at this time.

We conducted a separate search on Pubmed for heads-to-head trial comparing macrolides azithromycin with biologic agents for treatment of severe asthma and identified no such articles. See Table 2, Feasibility column.

Table 2. Key questions and Results for Duplication and Feasibility

Key Question	Duplication (01/2015-01/2018)	Feasibility (01/2013-01/2018)
KQ 1	Total number of identified systematic reviews: 0	<u>Size/scope of review</u> Relevant Studies Identified: 0 ○ Type: # 0 <u>Clinicaltrials.gov</u> <ul style="list-style-type: none">• Recruiting: 0• Active: 0• Complete: 0

Abbreviations: AHRQ=Agency for Healthcare Research and Quality; KQ=Key Question;

Summary of Findings

- Appropriateness and importance: The topic is both appropriate and important.
- Duplication: We did not identify systematic reviews that compared azithromycin to biologic agents. However we identified four completed and in-process systematic reviews that are mentioned because they might be useful to the nominator.
- Impact: The impact of a new systematic review would be high given the emergence of biologics as potentially effective therapeutics for severe asthma, and the lack of clear treatment guidelines on which patients would best benefit from azithromycin versus the newer biologics.
- Feasibility: A new review is not feasible given the lack of head to head trials assessing the comparative effectiveness of macrolides versus biologics in the prevention of exacerbation of severe asthma.

References:

1. National Heart, Lung, and Blood Institute. Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma-National Asthma Education and Prevention Program, Third Expert Panel on the Diagnosis and Management of Asthma. Washington, DC: National Heart, Lung, and Blood Institute; 2007.
2. National Heart, Lung, and Blood Institute. Advisory Council Asthma Expert Working Group. Needs Assessment Report for Potential Update of the Expert Panel Report-3 (2007): Guidelines for the Diagnosis and Management of Asthma. National Heart, Lung, and Blood Institute; 2015.
<https://www.nhlbi.nih.gov/sites/www.nhlbi.nih.gov/files/Asthma-Needs-Assessment-Report.pdf>.
3. Centers for Disease Control and Prevention. CDC. Most Recent Asthma Data. Atlanta, GA; 2014. http://www.cdc.gov/asthma/most_recent_data.htm July 25, 2016.
4. American Lung Association. Trends in Asthma Morbidity and Mortality; 2012. <http://www.lung.org/assets/documents/research/asthma-trend-report.pdf>[link is external]. Accessed on July 25, 2016.
5. Global Asthma Network .GAN. The Global Asthma Report 2014. Auckland, New Zealand; 2014.
http://www.globalasthmareport.org/resources/Global_Asthma_Report_2014.pdf[link is external].
6. Centers for Disease Control and Prevention. CDC. FastStats; 2017.
<http://www.cdc.gov/nchs/fastats/asthma.htm>. Accessed on January 19, 2018.
7. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, Adcock IM, Bateman ED, Bel EH, Bleecker ER, Boulet LP, Brightling C, Chaney P, Dahlen SE, Djukanovic R, Frey U, Gaga M, Gibson P, Hamid Q, Jajour NN, Mauad T, Sorkness RL, Teague WG. Eur Respir J. 2014 Feb;43(2):343-73. doi: 10.1183/09031936.00202013. PMID:24337046
8. Cai Y, Chai D, Wang R, Bai N, Liang BB, Liu Y. Effectiveness and safety of macrolides in cystic fibrosis patients: a meta-analysis and systematic review. Journal of Antimicrobial Chemotherapy 2011;66(5):968-78.
9. Spagnolo P, Fabbri LM, Bush A. Long-term macrolide treatment for chronic respiratory disease. European Respiratory Journal 2013;42(1):239-51.
10. Spagnolo P, Fabbri LM, Bush A. Long-term macrolide treatment for chronic respiratory disease. European Respiratory Journal 2013;42(1):239-51.

11. Guilbert, Theresa W, and Loren C Denlinger. "Role of Infection in the Development and Exacerbation of Asthma." *Expert review of respiratory medicine* 4.1 (2010): 71–83. PMC. Web. 12 Feb. 2018.
12. Kathy Low, Philip G. Bardin, Targeted Therapy for Severe Asthma: Identifying the Right Patients, *Molecular Diagnosis & Therapy*, 2017, 21, 3, 235.
13. Kew KM, Undela K, Kotorts I, Ferrara G. Macrolides for chronic asthma. *Cochrane Database of Systematic Reviews* 2015, Issue 9. Art. No.: CD002997. DOI: 10.1002/14651858.CD002997.pub4.
14. Normansell R, Walker S, Milan SJ, Walters EH, Nair P. Omalizumab for asthma in adults and children. *Cochrane Database of Systematic Reviews* 2014, Issue 1. Art. No.: CD003559. DOI: 10.1002/14651858.CD003559.pub4.
15. Farne HA, Wilson A, Powell C, Bax L, Milan SJ. Anti-IL5 therapies for asthma. *Cochrane Database of Systematic Reviews* 2017, Issue 9. Art. No.: CD010834. DOI: 10.1002/14651858.CD010834.pub3.
16. Edwards M, Gallagher A, Nair P, Drew S, Vyas A, Sharma R, Marsden PA, Evans DJW. Anti-interleukin-13 and anti-interleukin-4 agents versus placebo, anti-interleukin-5 or anti-immunoglobulin-E agents, for children and adults with asthma (Protocol). *Cochrane Database of Systematic Reviews* 2018, Issue 1. Art. No.: CD012929. DOI: 10.1002/14651858.CD012929.

Appendix A. Selection Criteria Summary

Selection Criteria	Assessment
1. Appropriateness	
1a. Does the nomination represent a health care drug, intervention, device, technology, or health care system/setting available (or soon to be available) in the U.S.?	Yes
1b. Is the nomination a request for a systematic review?	Yes
1c. Is the focus on effectiveness or comparative effectiveness?	Comparative effectiveness
1d. Is the nomination focus supported by a logic model or biologic plausibility? Is it consistent or coherent with what is known about the topic?	Yes
2. Importance	
2a. Represents a significant disease burden; large proportion of the population	Yes
2b. Is of high public interest; affects health care decision making, outcomes, or costs for a large proportion of the US population or for a vulnerable population	Yes
2c. Represents important uncertainty for decision makers	Yes
2d. Incorporates issues around both clinical benefits and potential clinical harms	Yes
2e. Represents high costs due to common use, high unit costs, or high associated costs to consumers, to patients, to health care systems, or to payers	Yes
3. Desirability of a New Evidence Review/Duplication	
3. Would not be redundant (i.e., the proposed topic is not already covered by available or soon-to-be available high-quality systematic review by AHRQ or others)	We identified no systematic reviews on the comparison of interest to the nominator.
4. Impact of a New Evidence Review	
4a. Is the standard of care unclear (guidelines not available or guidelines inconsistent, indicating an information gap that may be addressed by a new evidence review)?	Yes, the standard of care is unclear
4b. Is there practice variation (guideline inconsistent with current practice, indicating a potential implementation gap and not best addressed by a new evidence review)?	Guidelines are limited
5. Primary Research	
5. Effectively utilizes existing research and knowledge by considering: - Adequacy (type and volume) of research for conducting a systematic review - Newly available evidence (particularly for updates or new technologies)	We identified no studies on the comparison of interest to the nominator.

Abbreviations: AHRQ=Agency for Healthcare Research and Quality; KQ=Key Question;

Appendix B. Search for Evidence Reviews (Duplication)

Listed are the sources searched.

Search date: January 2015 to January 19, 2018

AHRQ: Evidence reports and technology assessments, USPSTF recommendations
VA Products: PBM, and HSR&D (ESP) publications, and VA/DoD EBCPG Program
Cochrane Systematic Reviews and Protocols <http://www.cochranelibrary.com/>
PubMed
PubMed Health <http://www.ncbi.nlm.nih.gov/pubmedhealth/>
HTA (CRD database): Health Technology Assessments <http://www.crd.york.ac.uk/crdweb/>
PROSPERO Database (international prospective register of systematic reviews and protocols)
<http://www.crd.york.ac.uk/prospero/>
CADTH (Canadian Agency for Drugs and Technologies in Health) <https://www.cadth.ca/>
DoPHER (Database of promoting health effectiveness reviews)
<http://eppi.ioe.ac.uk/webdatabases4/Intro.aspx?ID=9>
ECRI institute <https://www.ecri.org/Pages/default.aspx>

Secondary Sources checked on an as needed basis

Campbell Collaboration <http://www.campbellcollaboration.org/>
McMaster Health System Evidence <https://www.healthsystemsevidence.org/>
Robert Wood Johnson <http://www.rwjf.org/>
Systematic Reviews (Journal) : protocols and reviews
<http://systematicreviewsjournal.biomedcentral.com/>
UBC Centre for Health Services and Policy Research <http://chspr.ubc.ca/>
WHO Health Evidence Network <http://www.euro.who.int/en/data-and-evidence/evidence-informed-policy-making/health-evidence-network-hen>
CINAHL (EBSCO)

Appendix C. Search Strategy (Feasibility)

All Searches were done on Jan 19, 2018

- ("azithromycin"[MeSH Terms] OR "azithromycin"[All Fields]) OR ("macrolides"[MeSH Terms] OR "macrolides"[All Fields]) AND ("asthma"[MeSH Terms] OR "asthma"[All Fields]) AND (Clinical Trial[ptyp] AND "2013/02/14"[PDat] : "2018/02/12"[PDat] AND "humans"[MeSH Terms])
- ("omalizumab"[MeSH Terms] OR "omalizumab"[All Fields]) AND ("asthma"[MeSH Terms] OR "asthma"[All Fields]) AND (Clinical Trial[ptyp] AND hasabstract[text] AND "2013/02/14"[PDat] : "2018/02/12"[PDat] AND "humans"[MeSH Terms])
<clinicaltrials.gov link>
- ("asthma"[MeSH Terms] OR "asthma"[All Fields]) AND ("mepolizumab"[Supplementary Concept] OR "mepolizumab"[All Fields]) OR ("reslizumab"[Supplementary Concept] OR "reslizumab"[All Fields]) OR ("benralizumab"[Supplementary Concept] OR "benralizumab"[All Fields]) OR ("SAR231893"[Supplementary Concept] OR "SAR231893"[All Fields] OR "dupilumab"[All Fields]) AND (Clinical Trial[ptyp] AND hasabstract[text] AND "2013/02/14"[PDat] : "2018/02/12"[PDat] AND "humans"[MeSH Terms])