Biologic Drugs to Treat Asthma and Chronic Spontaneous Urticaria

Final Report

Executive Summary

April 2018

This report is intended only for state employees in states participating in the Drug Effectiveness Review Project (DERP). Do not distribute outside your state Medicaidagency and public agency partners.

Background

This report covers omalizumab, an anti-IgE monoclonal antibody approved to treat uncontrolled allergic asthma and chronic spontaneous urticaria resistant to antihistamines, and IL-5 monoclonal antibodies reslizumab, mepolizumab, and benralizumab, approved to treat severe asthma in patients with an eosinophilic asthma phenotype.

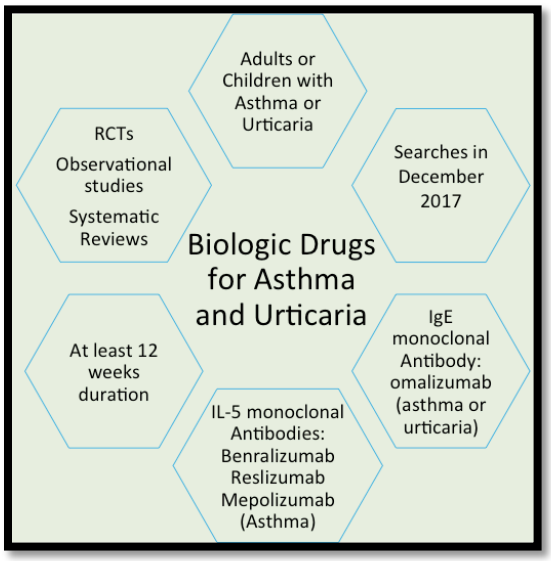
Asthma affects over 300 million people worldwide. Management of asthma is multifactorial with step-wise addition of medications determined by the frequency and severity of asthma symptoms. Steps range from 1 (intermittent asthma) to 5 (severe persistent asthma. Patients with uncontrolled Severe Step 5 asthma are potential candidates for biologic therapies, after confirming adherence and good inhaler technique. Phenotyping asthma (biologic markers and clinical history) can help identify patients who may benefit from biologic therapies. Eosinophilic inflammation identifies Type 2-high asthma, which may respond to anti-IL5 monoclonal antibodies that reduce eosinophils. Blood eosinophils are used as a surrogate marker for elevated sputum levels (>3%), but a reliable threshold has not been established. Studies have used thresholds of >150 cells/μL - ≥400 cells/μL. Patients with atopic (allergic) asthma, identified via skin testing, may benefit from the anti-IgE monoclonal antibody omalizumab.

Chronic spontaneous urticaria (CSU) is defined as recurrent episodes of hives (urticaria), with or without angioedema, that last 6 weeks or more. CSU affects 1% to 2% of the US population and typically lasts 2 to 5 years. In most patients there is no known allergic cause, although external factors can aggravate the symptoms. Treatment depends largely on 2nd generation H-1 antihistamines, including higher doses and dual antihistamine therapy. Oral corticosteroids are avoided, and omalizumab is reserved for refractory cases.

Key Questions

1. Are there differences in effectiveness and adverse event outcomes of biologic medications compared with each other or placebo when added to other treatments for outpatients with asthma?
    a. Are there subgroups of patients (e.g. elevated baseline eosinophils) for which biologic medications differ in benefits or harms?
2. Are there differences in effectiveness and adverse event outcomes of biologic medications compared with each other or placebo when added to other treatments for outpatients with chronic spontaneous urticaria?
    a. Are there subgroups of patients for which biologic medications differ in benefits or harms?

Inclusion Criteria



Overview of Included Evidence

There was no evidence directly comparing the drugs; all studies were placebo-controlled, add-on therapy. Using systematic reviews and newer trials, we included 15 trials of anti-IL-5drugs, 21 of omalizumab in asthma; and 7 trials in CSU. Most studies were good and fair quality.

Key Findings: Asthma

Drug (vs. Placebo)	Exacerbations –steroids	Exacerbations – ER/hospital	Quality of Life	Serious Harms	Subgroup analyses
IL-5 Monoclonal Antibodies					
Benralizumab: Summary	↓ +++	↓ ++	☒ +++	↓ ++	Exacerbation and Quality of life findings significant for eosinophils ≥ 150 cells/µl, but not for < 150.
Relative effects	Rate ratio 0.62 (0.55 to 0.70)	Rate ratio 0.68 (0.47 to 0.98) a	NA	RR 0.78 (0.64 to 0.96)	
Absolute effects	0.37 fewer events per patient per year (0.44 fewer to 0.29 fewer)	0.04 fewer events per patient per year (0.06 fewer to 0.002 fewer)[a]	Mean difference 0.23 (0.11 to 0.35)[a,b]	11% vs. 14%	
Reslizumab: Summary	↓ ++	☒ ++	☒ +++	☒ ++	Asthma control improved significantly in patients with higher eosinophils, worse symptoms, longer disease duration or nasal polyps. Single study of non-eosinophilic patients found no benefit.
Relative effects	Rate ratio 0.43 (0.33 to 0.55)	Rate Ratio 0.67 (0.39 to 1.17)	NA	RR 0.81 (0.57-1.75)	
Absolute effects	0.93 fewer events per patient per year (1.09 fewer to 0.73 fewer)	0.04 fewer events per patient per year (0.07 fewer to 0.02 more)	Mean Difference 0.28 (0.17, 0.39) b	7.6% vs.9.3%	
Mepolizumab: Summary	↓ +++	↓ +++	↑+++	☒ +	All patients studied had eosinophilia Exacerbation rates decreased significantly regardless of the number or type of other controller therapies used
Relative effects	Rate ratio 0.45 (0.36 to 0.55)	Rate ratio 0.36 (0.20 to 0.66)	NA	RR 0.50 (0.24 to 1.05)	
Absolute effects	0.81 fewer events per patient per year (0.66 fewer to 0.94 fewer)	0.10 fewer events per patient per year (0.05 fewer to 0.12 fewer)	Mean difference -7.40 (-9.50 to -5.29) [c]	6.0% vs. 12%,	
Anti-IgE Monoclonal Antibody: Omalizumab					
Omalizumab Summary	↓ ++ (steroid, ER, hospital)	NA	☒ ++	↓ ++	Reduction in exacerbations is significant in moderate to severe asthma, not in severe asthma
Relative effects	OR 0.55 (95% CI 0.42 - 0.60)	NA	NA	OR 0.72 (95% CI 0.57 - 0.91)	
Absolute effects	16% vs. 26%,	NA	Mean difference 0.31 (95% CI 0.23 - 0.39)	4.5% vs. 6.4%,	

[a] in subgroup of patients with eosinophils > 300 cells/µl; [b] Asthma Quality of Life Questionnaire (AQLQ); difference is statistically significant, but does not meet clinical importance threshold of 0.5 points; [c] St. Georges Quality of Life Scale; meets clinical importance threshold of 4 points.

+++, High confidence in findings; ++, Moderate confidence in findings; +, Low confidence in findings, ↓Decrease in outcome compared with placebo, ↑Increase in outcome compared with placebo, ☒No difference in outcome versus placebo

Key Findings: Chronic Spontaneous Urticaria

Omalizumab resulted in significantly more patients having complete response (8 RCTs, high SOE). Quality of life improved statistically, but did not reach clinically important differences (4 RCTs, high SOE). There were no differences in adverse event outcomes (4 RCTs, low SOE).

Key Findings: Urticaria

Outcome	Finding	Absolute & Relative Effects
Complete Response	↑+++	35.6% versus 4.1% OR 15.30 (4.27 to 54.90)
Quality of Life[a]	☒ +++	-9.2 versus –5.6 WMD -3.38 (-4.42 to -2. 34)
Serious AEs	☒ +	4.8% versus 4.4% RR 0.80 (0.24 to 2.65)
AE Withdrawals	☒ +	1.0% versus 0.9% RR 1.03 (0.24 to 4.41)

AE, adverse events; OR, odds ratio; RR, relative risk, WMD, weighted mean difference
a Does not meet threshold for clinical importance; difference of 4-5 points
+++, High confidence in findings; ++, Moderate confidence in findings; +, Low confidence in findings, ↓Decrease in outcome with o compared with placebo, ↑Increase in outcome compared with placebo, ☒No difference in outcome versus placebo

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DERP Systematic Review Methods

We followed systematic review methodology and procedures developed specifically for the Drug Effectiveness Review Project (DERP) and that are in accordance with current guidance for systematic reviews; for example, using dual review for study inclusion, quality assessments, and data abstraction. We searched MEDLINE through December 2017 and the Cochrane randomized trial database through 4th quarter, 2017. We requested dossiers of study information from manufacturers of included drugs. We created evidence tables, strength of evidence tables, and updated meta-analyses found in systematic reviews with newer trial data. Additional details on our methods can be found in Appendix A of the full report.

Conclusions

The body of evidence consisted of 15 placebo-controlled RCTs, 5 systematic reviews (of 28 RCTs), and 2 observational studies that were mostly fair to good quality. There were no trials directly comparing the anti-IL-5 drugs with each other. In patients with severe asthma, with elevated eosinophils, there was high-strength evidence that anti-IL-5 drugs benralizumab and mepolizumab reduce the incidence of asthma exacerbations requiring oral corticosteroids or an emergency department visit or hospitalization. Additionally, benralizumab and mepolizumab result in patients using lower doses of oral corticosteroids. Reslizumab reduced exacerbations requiring oral corticosteroids. In patients with allergic asthma, there was low- to moderate-strength evidence that omalizumab significantly reduces the incidence of asthma exacerbations, including those requiring oral corticosteroids or emergency department or hospital admission. In patients with chronic spontaneous urticaria, high-strength evidence found that omalizumab significantly improves the chance for complete response. High-strength evidence found that while quality of life was improved with these biologic drugs, the difference did not reach clinical importance except for mepolizumab. Adverse event evidence was lower strength; lower rates of serious adverse events were seen with benralizumab and omalizumab in asthma, but no differences were found for other drugs or in patients with urticaria.

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