Biologic Drugs to Treat Asthma and Chronic Spontaneous Urticaria

Original Report

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Overview

- We included 1 systematic review of IL-5 inhibitors and an additional 2 trials of benralizumab, 3 trials of mepolizumab, and 2 trials reslizumab in patients with eosinophilic asthma; 2 systematic reviews and an additional 12 trials of omalizumab in patients with allergic asthma; and 1 systematic review and 1 trial of omalizumab in patients with chronic spontaneous urticaria. The majority of studies were fair quality.

Key Findings

- Benralizumab reduced exacerbations requiring systemic corticosteroids and/or emergency department treatment or hospital admission (4 RCTs, high SOE). Quality of life improved more with benralizumab than placebo, but the difference was not clinically significant (4 RCTs, high SOE). There were fewer serious adverse events with benralizumab (5 RCTs, moderate SOE), but withdrawals due to adverse events did not differ (4 RCTs, moderate SOE). Baseline eosinophilia, using thresholds of either 300 or 150 cells/µL, did not change the effect of benralizumab on any outcome studied.
- Reslizumab significantly reduced asthma exacerbations requiring oral corticosteroid use in adults with eosinophilic asthma, but did not those requiring emergency department or hospital admissions (3 RCTs, moderate SOE). Quality of life was statistically better with reslizumab, but the difference may not be clinically important (4 RCTs, moderate SOE). There were no differences in adverse event outcomes (4 RCTs, moderate SOE).
- Exacerbations requiring systemic corticosteroids and/or emergency department treatment or hospital admission were significantly less likely with mepolizumab than placebo (3 RCTs, high SOE). Quality of life improved more with mepolizumab, and the difference was both statistically and clinically significant (3 RCTs, high SOE). There was no statistically significant difference in serious adverse events with added mepolizumab (3 RCTs, low SOE).
- Omalizumab significantly reduced medically serious asthma exacerbations in adults or children with moderate to severe allergic asthma, but did not significantly reduce exacerbations in patients with severe allergic asthma (11 RCTs, low to moderate SOE). These findings were confirmed in studies with longer follow-up (>52 weeks) and studies of only children with moderate to severe allergic asthma.
    - Pre-treatment with 4-5 doses of omalizumab reduced seasonal exacerbations in children with histories of frequent seasonal exacerbations (2 RCTs, low SOE).
    - Withdrawing omalizumab treatment after long-term use for moderate to severe allergic asthma resulted in significantly more asthma exacerbations over 52 weeks (1 RCT).
- Quality of life was statistically improved with omalizumab in patients with moderate to severe allergic asthma, but the difference may not be clinically important (7 RCTs, moderate SOE).

- Serious adverse events (including asthma exacerbations) were significantly less frequent with omalizumab while withdrawal due to adverse events did not differ between omalizumab and placebo. Omalizumab resulted in more injection-site reactions. Observational evidence on the risk of malignancy and arterial thromboembolic events with omalizumab were insufficient to draw conclusions, and further research is needed.
- Significantly more patients were able to discontinue or reduce the dose of inhaled corticosteroids with omalizumab. Evidence on oral corticosteroids was too limited to draw conclusions.
- Omalizumab resulted in significantly more patients with chronic spontaneous urticaria having complete response (8 RCTs, high SOE). Evidence on quality of life was limited, but indicated improvement with omalizumab. There were no differences in adverse event outcomes.

Background

The biologic drugs reviewed in this report include omalizumab, an anti-IgE monoclonal antibody drug US Food and Drug Administration (FDA)-approved to treat allergic asthma resistant to other treatments, including corticosteroids, and chronic spontaneous urticaria in patients resistant to other treatments, such as antihistamines. Skin testing to establish an allergic link is typically required. The other drugs reviewed are the interleukin-5 inhibitor monoclonal antibody drugs reslizumab, mepolizumab, and benralizumab, which are FDA-approved to treat severe asthma in patients with an eosinophilic phenotype of asthma. Off-label uses in other allergic or inflammatory conditions have been studied, and are briefly reviewed in this report.

Asthma is a chronic disease of the airways characterized inflammation, excessive bronchoconstriction causing variable airflow obstruction, and airway remodeling. Patients experience shortness of breath, wheezing, chest tightness, and cough.[1,2] The prevalence of asthma is estimated to effect over 300 million people worldwide.[2] While the prevalence increased dramatically in the early 1980's up to the mid-1990's (a 42% increase), the rate has slowed to a 7.8% to 8.2% increase from 2001 through 2009.[3] In children, more recent data indicate a plateau in prevalence rates, except among minority or low socioeconomic groups.[4]

Management of asthma is multifactorial and involves monitoring, avoiding or managing triggers of asthma, and pharmacologic treatment. Pharmacological treatment starts with determining the frequency - intermittent (Step 1) or persistent asthma symptoms. Persistent asthma is divided into mild (Step 2), moderate (Step 3), and severe (Steps 4 and 5). Each step has preferred controller-drug treatments, according to the National Asthma Education and Prevention Program: Expert panel report III.[1]

In recent years, the recognition that asthma is not a single disease, but multiple, overlapping, phenotypes of disease has changed the way asthma is viewed, categorized, and treated.[5,6] Phenotyping asthma, based on biologic markers and clinical picture, may help to target treatments better. Phenotypes suggested for patients with severe asthma are early-onset allergic (atopic); late-onset, eosinophil predominant; and late-onset, neutrophil predominant. Omalizumab, the anti-IgE monoclonal antibody drug, is targeted to patients with atopic asthma, while the IL-5 inhibitors target patients with elevated bronchial eosinophils (typically noted as >3% in sputum samples). The threshold for identifying elevated blood eosinophils that are a reliable marker for elevated sputum eosinophils is not entirely clear, but studies have used blood levels of >150 cells/μL to ≥400 cells/μL.

Chronic spontaneous urticaria (CSU), also known as chronic idiopathic urticaria, is defined as recurrent episodes of hives (urticaria), with or without angioedema, that lasts for 6 weeks or longer. 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, including use of non-steroidal anti-inflammatory drugs. Present angioedema can involve the lips, cheeks, periorbital areas, extremities, and genitals. A small percentage of patients also have systemic symptoms, such as headache. Treatment depends largely on antihistamines, including higher doses and dual antihistamine therapy, with use of H-2 antagonists and systemic steroids in refractory cases.

Key Questions

1. What is the comparative efficacy and effectiveness of biologic medications used to treat outpatients with asthma?
2. What is the comparative tolerability and frequency of adverse events of biologic medications used to treat outpatients with asthma?
3. Are there subgroups of patients (e.g., groups defined by demographics [age, racial groups, gender], asthma severity, comorbidities, other medications [drug-drug interactions], smoking status, genetics, or pregnancy) for which biologic medications used to treat asthma differ in efficacy, effectiveness, or frequency of adverse events?
4. What is the evidence on the benefits and harms of using these biologic drugs to treat with chronic spontaneous urticaria?

Methods

We followed systematic review methodology and procedures developed specifically for the Drug Effectiveness Review Project (DERP)[5] 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.

Inclusion Criteria

Populations

- Adults or children with persistent or chronic asthma
- Adults with CSU

Interventions

Table 1. Included Drugs

Generic Name	Trade Name	FDA Approval Year	Mechanism of Action	Route of Administration
Benralizumab	Fasenra™	2017	IL-5 antagonist monoclonal antibody	Subcutaneous injection every 8 weeks
Reslizumab[a]	Cinqair®	2016	IL-5 antagonist monoclonal antibody	Intravenous infusion every 4 weeks
Mepolizumab[b]	Nucala®	2015	IL-5 antagonist monoclonal antibody	Subcutaneous Injection every 4 weeks[d]
Omalizumab[c]	Xolair®	2003	Anti-IgE monoclonal antibody	Subcutaneous Injection every 2-4 weeks[d]

Abbreviations: FDA, US Food and Drug Administration; IgE, immunoglobulin E; IL, interleukin.
[a] *Approved in patients 18 years of age and older with an eosinophilic phenotype.*
[b] *Approved in patients 12 years of age and older with an eosinophilic phenotype.*
[c] *Approved in patients 6 years of age and older with moderate to severe persistent asthma.*
[d] *Not patient-administered.*

Comparisons

- Placebo- or usual care-controlled (including add-on studies)
- IL-5 inhibitors versus each other

Efficacy and Effectiveness Outcomes

Asthma (Key Questions 1-3):

- Asthma exacerbations, symptom control, oral steroid use, quality of life assessed using validated scales, emergency department or hospital admissions, decreasing mortality

Chronic Spontaneous Urticaria (Key Question 4):

- Response (e.g., Urticaria Activity Score [UAS7]≤6) or complete response (UAS7=0), symptoms (e.g., itching), quality of life assessed using validated scales, use of other anti-urticaria medications

Adverse Event Outcomes

- Withdrawals due to adverse events and serious adverse events
- Specific adverse events (e.g., injection site pain, angioedema, anaphylaxis, cancer)

Study Designs

- Randomized controlled clinical trials of at least 12 weeks duration
- Recent (searches within 3 years) good-quality systematic reviews
- Observational studies of at least 6 months duration and N≥1,000 for serious adverse events

Setting

- Outpatients (prior hospitalization and drug administration in an inpatient setting not excluded)

Findings

Overview

After comprehensive searching, we screened 1,603 publications and 10 manufacturer dossiers and ultimately included 19 trials (reported in 29 publications), 2 observational studies (in 4 publications), and 4 systematic reviews that included another 30 randomized controlled trials (RCTs), including 10,573 patients. We included 1 systematic review of IL-5 inhibitors (benralizumab, mepolizumab, and reslizumab) and an additional 2 trials of benralizumab (in 3 publications), 3 trials of mepolizumab (in 4 publications), and 2 trials reslizumab (in 2 publications), in patients with eosinophilic asthma. We included 2 systematic reviews, an additional 12 trials (in 19 publications), and 2 observational studies (in 4 publications) of omalizumab in patients with allergic asthma. Finally, we included 1 systematic review and 1 trial (2 publications) of omalizumab in patients with CSU. The majority of studies were fair quality. The results are organized by drug class, and then population. The most recently approved drugs are reviewed first.

Please refer to Appendix D for all included studies, Appendix E for a list of studies excluded after full-text review with reasons for exclusion, Appendix F for strength of evidence rations, and Evidence Tables for quality assessment and results of included studies.

Interluekin-5 Inhibitors in Adults with Severe Eosinophilic Asthma

Benralizumab

We included a good-quality Cochrane systematic review of all 3 IL-5 inhibitors in adults and children with moderate to severe asthma.[7] For benralizumab, the review included 4 good-quality trials (N=2,648) of 20 mg or 30 mg benralizumab every 4 and every 8 weeks with 48 to 56 weeks of follow-up. The only subgroup analyses were variation in findings based on baseline eosinophil levels, using a threshold of 300 cells/μL.

In addition to the review, we included an RCT published after the review, and a subgroup analysis of 2 RCTs included in the review. The good-quality ZONDA trial (N=220) of adults with severe asthma randomized patients to 30 mg of benralizumab or to placebo given every 4 weeks for 28 weeks, or every 4 weeks for the first 12 weeks, then every 8 weeks for the remaining 16 weeks of the trial (abbreviated below as every 8 weeks).[8] A subgroup analysis of 2 trials included in the Cochrane review, SIROCCO and CALIMA, (subgroup n=1,456, Total N=2,510) included adults given benralizumab or placebo every 8 weeks, excluding the children and patients treated every 4 weeks.[9] Both trials enrolled patients with severe uncontrolled asthma; duration of treatment was 48 weeks in SIROCCO, and 56 weeks in CALIMA. The analyses examined the effect of baseline eosinophil levels of ≥150 cells/μL and <150 cells/μL on outcomes (lower than that analyzed in the Cochrane review). Most patients (86% across both trials) had eosinophil levels ≥150 cells/μL.

Key Outcomes for this Review

Asthma Exacerbations

The Cochrane review[7] defined "clinically significant" asthma exacerbations as those requiring oral corticosteroids for 3 or more days. These exacerbations were significantly less likely with benralizumab than placebo (3 RCTs, N=2456; rate ratio 0.62, 95% CI 0.55 to 0.70). There was no significant difference in the effect between patients with eosinophilic and non-eosinophilic phenotypes (≥or <300 cells/μL; P=0.22 for subgroup difference). The ZONDA trial also showed lower exacerbation rates with benralizumab compared with placebo, with exacerbations defined as increased systemic steroids, emergency department treatment, or hospitalization for asthma. (Appendix F, Table F-1).[8]

Exacerbations requiring emergency department or hospital admission were significantly less likely with benralizumab (2 RCTs, N=1537; rate ratio 0.68, 95% CI 0.47 to 0.98) in patients with eosinophilia (≥300 cells/μL).[7] The same was true in the ZONDA trial,[8] for benralizumab given either every 4 weeks (rate ratio 0.45, 95% CI 0.27 to 0.76) or every 8 weeks (rate ratio 0.30, 95% CI 0.17 to 0.53), each compared with placebo. Our confidence in these findings is high; future studies are unlikely to alter the findings.

Table 2 shows the results of the subgroup analyses from the SIROCCO and CALIMA trials.[9] Patients with baseline blood eosinophil levels ≥150 had significantly lower exacerbation rates than placebo, while the decrease was not significant in patients with lower eosinophil levels, though this may reflect the smaller numbers of such patients.

Table 2. Effect of Baseline Eosinophils on Key Outcomes in the SIROCCO and CALIMA Trials[9]

Outcome	Trial	Baseline Blood Eosinophils (cells/µL)	N	RR[a] (benralizumab vs. placebo)	95% Confidence Interval
Exacerbations	SIROCCO	≥ 150	631	**0.58**	**0.46 to 0.74**
		< 150	122	0.76	0.45 to 1.27
	CALIMA	≥ 150	615	**0.64**	**0.50 to 0.81**
		< 150	88	0.65	0.39 to 1.09
				LSMD[b] (benralizumab vs. placebo)	
Quality of life[c]	SIROCCO	≥ 150	631	**0.19**	**0.01 to 0.37**
		< 150	122	0.46	-0.01 to 0.94
	CALIMA	≥ 150	615	**0.20**	**0.02 to 0.38**
		< 150	88	-0.01	-0.48 to 0.47
				RR[a] (benralizumab vs. placebo)	
Serious adverse events	Both trials	≥ 150	1246	0.86	0.64 to 1.14
	SIROCCO	< 150	122	1.19	0.57 to 2.43
	CALIMA	< 150	88	**0.28**	**0.086 to 0.88**

Bold indicates a statistically significant difference in outcome between patients given benralizumab and those given placebo within a subgroup.
[a]Rate ratio (exacerbations) or relative risk (SAEs); a value of 1.0 indicates no difference between benralizumab and placebo. The EPC calculated relative risks for serious adverse events, pooled across the SIROCCO and CALIMA trials for patients with baseline eosinophils ≥150/µL. For those with baseline eosinophils < 150/µL, statistical heterogeneity prevented pooling (I^2=75%).
[b]Least squares mean difference; a value of 0 indicates no difference between benralizumab and placebo.
[c]AQLQ(S) + 12, the Standardized Asthma Quality of Life Questionnaire for 12 years and older

Quality of Life

Three good-quality trials (N=1541) of patients with eosinophilic asthma[7] measured quality of life using the Asthma Quality of Life Questionnaire (AQLQ), a scale of 1 to 7 with higher scores indicating better quality of life. The difference in AQLQ score was greater with benralizumab treatment than with placebo (mean difference 0.23, 95% CI 0.11 to 0.35). This difference was statistically significant, but less than the minimum clinically significant difference in AQLQ score of 0.5 or more. The ZONDA trial[8] showed similar, statistically significant improvements in quality of life for patients treated with benralizumab compared with those given placebo (Appendix F, Table F-1). Our confidence in these findings is high; future studies are unlikely to alter the findings.

Table 2 shows the effect of benralizumab on quality of life according to baseline eosinophil levels.[9] Patients with ≥150 cells/µL eosinophils had significant improvements in quality of life. Results for patients with <150 cells/µL blood eosinophils at baseline were not significant, but suffered from small sample sizes.

Serious Adverse Events

Updating the Cochrane meta-analysis of 4 good quality RCTs[7] with data from the ZONDA trial,[8] we found significantly fewer serious adverse events with benralizumab (5 RCTs, relative risk 0.78, 95% CI 0.64 to 0.96). This is likely due to the inclusion of asthma exacerbations as serious adverse events. We have moderate confidence in this result; future studies might alter the findings.

Based on analyses in the Cochrane review and the subgroup analyses of the SIROCCO and CALIMA trials (Table 2), serious adverse event results did not differ by baseline eosinophilia (defined as either >300 or >150 cells/µL).

Withdrawals due to Adverse Events

Updating the Cochrane meta-analysis of 4 good-quality RCTs[7] with data from the ZONDA trial,[8] there was no significant difference in withdrawals due to adverse events (5 RCTs, 2.2% vs. 1.0%, relative risk 1.84, 95% CI 0.92 to 3.68). We have moderate confidence in this result; future studies could alter the findings. There was no statistically significant difference in results between patients with and without eosinophilia in the Cochrane analysis (P=0.88 for subgroup difference).[7]

Injection Frequency

Evidence comparing different frequency regimens for benralizumab is limited, with no direct comparative analyses. The Cochrane review included 2 trials of benralizumab with injection frequencies of both 4 weeks and 8 weeks, and listed these treatment arms separately in meta-analyses.[7] For each study and outcome analyzed, confidence intervals for the 2 frequencies overlapped, suggesting no statistically significant difference in the effect of benralizumab given every 8 weeks compared with every 4 weeks. However, the review did not analyze the effect of injection frequency pooled across studies. The FDA-approved label for benralizumab states that the "recommended dose is 30 mg every 4 weeks for the first 3 doses, followed by once every 8 weeks thereafter," similar to the schedule used in the 8-week arm of the ZONDA trial.[8] As shown in Appendix Table F-1, the effect of benralizumab on asthma exacerbations and quality of life in ZONDA did not differ by treatment frequency (confidence intervals overlapped), supporting the conclusion that the 2 schedules have similar efficacy.

Secondary Outcomes

Change in Use of Oral Corticosteroids

The primary outcome in the ZONDA trial[8] was the percent reduction in oral corticosteroid dose from baseline to week 28. The median reduction in the placebo arm was 25%, while in each benralizumab arm the median reduction in dose was 75% (P<0.001).

Symptom Change

Three good-quality trials (N=2359) included in the Cochrane review reported asthma symptoms using the Asthma Control Questionnaire (ACQ). Scores on the ACQ range from 0 to 6, with lower

scores reflecting better asthma control and a change of 0.5 or more considered clinically important. Patients treated with benralizumab showed greater improvement in ACQ scores than those given placebo (mean difference -0.20, 95% CI -0.29 to -0.11), with no significant difference for patients with and without baseline eosinophilia (P=0.36).[7] In the ZONDA trial, ACQ scores for patients treated every 8 weeks with benralizumab decreased more than for patients given placebo (difference of -0.55 points, 95% CI -0.23 to -0.86), but there was no statistically significant difference for patients treated every 4 weeks.[8]

Injection Site Reactions

Injection site reactions were reported in the subgroup analyses of SIROCCO and CALIMA.[9] For all adult patients, there was no statistically significant difference in skin reactions for patients treated every 8 weeks with benralizumab compared with those given placebo (2.4% vs. 1.6%, relative risk 1.44, 95% CI 0.69 to 3.00). Results were similar for patients with baseline eosinophilia (≥150 cell/microliter) as well as for those with lower baseline eosinophil levels.

Reslizumab

We included a good-quality Cochrane systematic review of IL-5 Inhibitors for asthma, including reslizumab (Evidence Tables 5 and 6).[7] The review included 4 placebo-controlled RCTs of reslizumab in adults with moderate to severe asthma. Three of these required that patients have blood eosinophils of ≥400 cells/μL (N=1164), while the fourth study was of patients with non-eosinophilic asthma. Patients in these studies were using medium doses of inhaled corticosteroids, and had a history of at least 1 clinically relevant asthma exacerbation in the past year. Reslizumab was given at 3 mg/kg intravenous every 4 weeks for 4 doses (2 RCTs) or 13 doses (2 RCTs). Two of the studies were good quality, and the others were fair quality. The results for studies of patients with eosinophilic asthma are presented here, where possible.

       Through our searches, we also identified an older study of reslizumab in a similar population that was excluded from the review because it was 12 weeks in duration (3 doses of reslizumab or placebo). The review required studies to be at least 16 weeks in duration.[10] This fair-quality RCT enrolled adults with moderate to severe asthma, poorly controlled, and with sputum eosinophils of ≥3% (N=106). The Cochrane review notes that studies evaluating blood and sputum eosinophil levels in individual patients have found that blood eosinophil levels of ≥400 cells/μL correlate well with sputum levels of ≥3%.

Key Outcomes for this Review

Asthma Exacerbations

In the Cochrane review, asthma exacerbations were reported as both those requiring oral corticosteroids and those requiring an emergency department visit or admission to hospital. Using the more conservative definition (requiring oral steroids), reslizumab significantly reduced the risk compared with placebo. The rate ratio was 0.43 (95% CI 0.33 to 0.55, 2 RCTs).[7] The 12-week study used a more broad definition of exacerbations, which included a >20% decrease in FEV1 as well.[10] The results did not reach statistical significance, but the absolute difference was large; 8% versus 19% (P=0.083).

       Based on the more serious definition of an exacerbation requiring an emergency department visit or hospital admission, reslizumab did not reduce the risk compared with

placebo. The Cochrane review conducted a meta-analysis of the exacerbations per patient-year, finding a rate ratio of 0.67 (95% CI 0.39 to 1.17, 2 RCTs, N=953),[7] and the additional study we identified also found no difference between groups (N=106, 5.7% versus 7.5%, P=0.70).[10]

Our confidence in these findings is moderate; future studies could potentially change the conclusions.

Quality of Life

Quality of life was typically measured using the AQLQ, and found to be significantly more improved with reslizumab than with placebo (mean difference 0.28, 95% CI 0.17 to 0.39, 2 RCTs).[7] Because the difference does not meet the established effect size of 0.5, it is unclear if the difference is clinically meaningful. The 12-week trial did not report on quality of life. Our confidence in these findings is high; future studies are unlikely to change the conclusions.

Serious Adverse Events

Based on 3 RCTs (N=1059), there were no differences between reslizumab and placebo in serious adverse events (EPC-calculated 7.6% versus 9.3%, relative risk 0.81, 95% CI 0.57 to 1.75). Our confidence in these findings is moderate; future studies could potentially change the conclusions.

Withdrawal due to Adverse Events

Based on 3 RCTs (N=1059), there were no differences between reslizumab and placebo in withdrawals due to adverse events (EPC-calculated 3.0% versus 4.4%, relative risk 0.67, 95% CI 0.37 to 1.20). Our confidence in these findings is moderate; future studies could potentially change the conclusions.

Secondary Outcomes

Symptom Change

The Cochrane review reported that symptoms were significantly improved with reslizumab compared with placebo using the ACQ, based on 4 RCTs (N=1652), with 1 that included non-eosinophilic patients (mean difference -0.25, 95% CI -0.33 to -0.17).[7] In the 12-week RCT (N=106), the difference between groups did not reach statistical significance (mean difference -0.38, 95% CI -0.76, 0.01), but the direction and size of effect is similar to the pooled analysis from the Cochrane review.[10] Subgroup analyses suggest that patients with higher baseline ACQ score, longer disease duration, and with nasal polyps improved more than those with lower baseline scores, shorter disease duration (<23 years), and without polyps.

Eosinophils

In a subgroup analysis of baseline levels of eosinophils in the 12-week trial, those with higher levels (>10% in sputum, and >500 cells/µL in blood) had a significant improvement in ACQ scores, while those with lower levels did not.[10] The Cochrane review did not evaluate the effect of differing levels of eosinophils on results, but a subgroup analysis of just 1 study of non-eosinophilic patients found that there was no significant benefit on the ACQ measure of symptoms in this group.

Mepolizumab

The Cochrane systematic review of IL-5 inhibitors included trials of both intravenous and subcutaneous mepolizumab.[7] We also identified another RCT of intravenous mepolizumab. That was not included in the Cochrane review.[11] Since only a subcutaneous formulation is approved in the United States, we excluded data from trials of intravenous mepolizumab. The Cochrane review included data from 2 good-quality trials of subcutaneous mepolizumab (N=1,127) in patients with severe eosinophilic asthma, and no subgroups were analyzed. Although the Cochrane review did not conduct subgroup analyses, we have included a published subgroup analysis of the MENSA study (1 of the 2 RCTs included in the Cochrane review) that reported efficacy according to the background controller therapy.[12] The Cochrane review excluded results from the SIRIUS trial[13] because its primary outcome was reduction in glucocorticoid use, but we included this and other outcomes from this good-quality trial of 135 patients with severe eosinophilic asthma.

Key Outcomes for this Review

Asthma Exacerbations
Clinically significant asthma exacerbations (those requiring oral corticosteroids) were significantly less likely in patients given mepolizumab than those given placebo (2 RCTs, N=936; rate ratio 0.45, 95% CI 0.36 to 0.55). The SIRIUS trial supported these findings, though this trial was smaller (N=135) and statistical significance was borderline (rate ratio 0.68, 95% CI 0.47 to 0.99). Based on 2 trials (N=936 patients), those treated with mepolizumab were significantly less likely to have exacerbations requiring emergency department treatment or hospital admission (rate ratio 0.36, 95% CI 0.20 to 0.66).[7] Our confidence in these findings is high, future studies are very unlikely to alter these findings.

The 32-week MENSA trial assessed mepolizumab added to standard of care using inhaled corticosteroids (ICSs) with 1 or more additional controller drugs, such as long-acting beta-agonists or tiotropium. All patients had severe eosinophilic asthma. A secondary analysis of trial results[12] showed decreased exacerbation rates with subcutaneous mepolizumab regardless of the number or type of other controller therapy used. The differences between mepolizumab and placebo were statistically significant for all but 1 of the subgroups analyzed (patients given an ICS along with 2 other therapies, for whom exacerbation rates decreased from 1.80 to 1.07 with added mepolizumab, rate ratio 0.68, 95% CI 0.42 to 1.09).

Quality of Life
Scores on the St. George's Respiratory Questionnaire (SGRQ) range from 0 to 100, with lower scores showing better quality of life. A change of 4 or more points is considered clinically significant.[7] Quality of life improved more for patients treated with mepolizumab than for those given placebo, according to both the Cochrane review (mean difference -7.40, 95% CI -9.50 to -5.29)[7] and the SIRIUS trial (mean difference -5.8, 95% CI -10.6 to -1.0).[13] Our confidence in these findings is high.

Serious Adverse Events
Serious adverse events (including asthma exacerbations) were less frequent with mepolizumab, but the difference was not statistically significant (3 RCTs, 6.0% vs. 12%, relative risk 0.50, 95% CI 0.24 to 1.05). There was moderate statistical heterogeneity in this pooled analysis (I^2=57%), due

to variation in the magnitude of effect across the trial arms. Because of this, our confidence in these findings is low; it could change with additional evidence.

Withdrawals due to Adverse Events

Few patients withdrew due to adverse events in the 2 trials in the Cochrane review or the SIRIUS trial (16 of 1,071 patients across the 3 trials), and evidence was insufficient to compare rates between mepolizumab and placebo (1.1% vs. 1.9%, relative risk 0.63, 95% CI 0.22 to 1.77).

Secondary Outcomes

Change in Use of Oral Corticosteroids

The SIRIUS trial's primary outcome was a reduction in oral glucocorticoid dose category, with 4 categories defined: 90% to 100% reduction, 75% to <90%, 50% to <75%, and >0% to <50%. The overall odds ratio for dose reduction by this definition was 2.39 for mepolizumab compared with placebo (95% CI 1.25 to 4.56). Table 3 shows actual changes in prednisone dose.

Table 3. Change in Dose of Prednisone in the SIRIUS Trial (mg/day)[13]

Time	Mepolizumab		Placebo	
	Mean dose	Median dose	Mean dose	Median dose
Baseline	12.4	10.0	13.2	12.5
Weeks 20-24	8.6	3.1	10.5	10.0

Symptom Change

Patients treated with mepolizumab showed greater improvement in ACQ scores than those given placebo in the 2 Cochrane trials (mean difference -0.42, 95% CI -0.56 to -0.28), though the difference was less than that considered clinically important (≥0.5).[7] The SIRIUS trial showed a difference in ACQ between mepolizumab and placebo that was statistically and clinically significant (-0.52, 95% CI -0.87 to -0.17).[13]

Injection Site Reactions

The low rate of injection site reactions in the SIRIUS trial did not allow meaningful comparisons across groups (4 reactions occurred in the mepolizumab group and 2 in the placebo group).[13]

Other Indications (off-label)

Mild-to-Moderate Asthma

In a RCT of 351 patients with mild-to-moderate asthma, benralizumab improved FEV1 outcomes at 12 weeks compared with placebo in patients with ≥300 cells/μL blood eosinophils at baseline.[14] Other clinical measures were not reported, and there was not a significant improvement in patients with <300 cells/μL. There were no differences between groups in adverse event outcomes. This study was funded by AstraZeneca.

Eosinophilic Esophagitis

An RCT of reslizumab or placebo given for 12 weeks in children and adolescents with biopsy-proven eosinophilic esophagitis (N=226) found no difference in the physician's global assessment of disease, even though eosinophils were significantly reduced.[15] There were no

significant differences in adverse event outcomes between groups. This study was funded by Ception Therapeutics, Inc.

IgE Antagonist: Omalizumab

Allergic Asthma

We included a good-quality Cochrane systematic review of omalizumab in patients with moderate to severe allergic asthma (Evidence Tables 5 and 6).[16] While the review included 25 RCTs in total, 10 (N=3,261) of these evaluated subcutaneous omalizumab every 2 to 4 weeks in patients also receiving stable doses of inhaled corticosteroids, while 5 (N=1634) had a 12- to 28-week period of stable oral or inhaled corticosteroid dose, followed by a period of attempted steroid-dose reduction. Dosing varied, ranging from 75 mg every 2 weeks to 375 every 4 weeks or was determined by weight and IgE-level (e.g., >0.016 mg/kg/IgE-IU/mL). The remaining studies were not relevant to this review for a variety of reasons. The studies ranged from 16 to 60 weeks in duration, included both adults and children, and most studies were fair quality. The review analyzed the studies according to whether they evaluated only a stable steroid dose, or if they evaluated stable-dose followed by dose-reduction of steroids, and according to severity of asthma (moderate to severe and severe only).

We additionally included 8 studies on omalizumab in patients with allergic asthma not included in this systematic review (Evidence Tables 1-4). Two RCTs evaluated quality of life in moderate to severe asthma patients treated with omalizumab in Brazil and China (N=732, 20 – 24 weeks of add-on therapy),[17,18] however, 1 of these was poor quality for the measurement of quality of life and was used only to evaluate harms of omalizumab.[17] Two fair-quality RCTs evaluated pre-treatment of children with a history of asthma exacerbations during fall or winter (N=526, 16 to 20 weeks of treatment prior to fall or winter seasons).[19,20] We also included 1 fair-quality RCT evaluating whether response at 16 weeks of treatment predicts continued response at 32 weeks in patients with severe allergic asthma (N=400),[21] and 1 fair-quality RCT evaluating whether the response achieved with omalizumab continues after discontinuation (N=176 patients with moderate-to-severe asthma, 52 weeks duration).[22] Finally, we included 2 observational studies (in 4 publications) evaluating harms of omalizumab therapy (N=10,225).[23-26]

Key Outcomes for this Review

Asthma Exacerbations

Because patients with allergic asthma typically have more frequent and more severe asthma exacerbations, the studies of omalizumab reported medically serious exacerbations – those requiring a hospitalization, an emergency department visit, or an office visit. These are not exacerbations that can be managed at home with rescue medications, such as inhaled short-acting beta-agonists. Based on 10 fair-quality RCTs (N=3261, all continuing inhaled corticosteroids), omalizumab resulted in a significant reduction in exacerbations when used every 2 to 4 weeks for 16 to 60 weeks in patients with allergic asthma (16% versus 26%, odds ratio 0.55, 95% CI 0.42 to 0.60).[16] Among the subgroup with moderate-to-severe asthma, the reduction was also significant (7 RCTs, OR 0.50, 95% CI 0.42 to 0.60), while in the subgroup with severe asthma there was not a significant reduction (2 RCTs, OR 1.0, 95% CI 0.5 to 1.99). Similarly, in a single small study of patients with severe asthma using both oral and inhaled

corticosteroids, omalizumab did not reduce the incidence of exacerbations (N=95, odds ratio 1.65, 95% CI 0.66 to 4.15).[16]

Limiting the analysis to studies of 52 weeks or longer, another fair-quality systematic review also found a reduction in serious exacerbations (21% with omalizumab versus 38% with placebo, relative risk 0.63, 95% CI 0.55 to 0.71).[27] Limiting the analysis to 3 RCTs (N=1381) of children (ages 6 to 20), the incidence of exacerbations was higher than in the overall population, but the reduction with omalizumab was also significant.[28] Twenty-seven percent of children taking omalizumab had an exacerbation, compared with 41% taking placebo (relative risk 0.69, 95% CI 0.59 to 0.80). Our confidence in these findings is moderate, meaning that future studies are less likely to change these findings. However, our confidence in findings for patients with severe asthma is low due to fewer studies, and future studies could change these findings.

Two RCTs (N=526) evaluated pre-treatment with omalizumab to reduce the increased risk of exacerbations in children during fall and winter. One study was a small pilot study,[19] while the other was a larger, well-funded study (PROSE),[29] and both were fair quality. The children enrolled had a history of increases in exacerbations during fall or winter, and had moderate to severe asthma. Omalizumab was given every 2 to 4 weeks for 4 or 5 months prior to the fall or winter season, in addition to "guidelines-based therapy". The exacerbation rate during the following fall or winter was reduced significantly with omalizumab (11% with omalizumab and 25% with placebo, pooled relative risk 0.44, 95% CI 0.28 to 0.72). Because of the few studies, our confidence in these findings is low, meaning that future studies could change the findings.

The other 2 RCTs that reported exacerbations were unusual. A fair-quality RCT (N=476) evaluated the impact of discontinuing omalizumab after long-term use (reported as about 5 years) for moderate to severe allergic asthma.[22] The patients were randomized to placebo or to continuing omalizumab and 84% were also using an inhaled corticosteroid. At 52 weeks, significantly fewer patients taking omalizumab (48%) had an exacerbation than those taking placebo (67%; adjusted odds ratio 0.44, 95% CI 0.23 to 0.82). Analysis of patients using an inhaled corticosteroid found similar results (adjusted odds ratio 0.39, 95% CI 0.20 to 0.76).

The second fair-quality RCT (N=400) evaluated whether response to omalizumab at 16 weeks predicted response at 32 weeks in patients with severe allergic asthma.[21] The primary outcome was a physician's global evaluation measure, not exacerbations. Exacerbations were reported only over the entire 32-week period and showed that significantly fewer patients continuing omalizumab had a severe exacerbation (24%) than those taking placebo (42%; relative risk 0.56, 95% CI 0.34 to 0.92). Other outcomes are reported below.

Quality of Life
Quality of life was typically measured using the AQLQ, and was found to be significantly improved with omalizumab in patients with moderate-to-severe allergic asthma (6 RCTs, mean difference 0.31, 95% CI 0.23 to 0.39), but this difference was small and was not found to meet the pre-specified clinically important effect size of 0.5.[16] Two more recent RCTs evaluated quality of life in moderate to severe asthma patients treated with omalizumab in Brazil and China (N=732, 20 to 24 weeks of add-on therapy),[17,18] however, the study conducted in China was poor quality for the measurement of quality of life.[17] The smaller Brazilian study (N=116) of patients with severe allergic asthma reported differences in AQLQ scores of 0.8 at 12 weeks, and 1.4 at 20 weeks (both P<0.001). This difference does meet the clinically relevant threshold of a ≥0.5-point

improvement. The study from Brazil also reported that significantly more patients had clinically relevant improvement on the AQLQ (≥0.5 points) with omalizumab than placebo at 20 weeks (71.6% versus 22.2%, P<0.001).[18] Our confidence in these findings is low, due to the inconsistency in clinical relevance, and the overall small numbers of patients assessed. Future studies could alter these findings; particularly, future studies could resolve the issue of statistically significant versus clinically significant differences.

Serious Adverse Events

All of the RCTs reported serious adverse events including asthma exacerbations. As a result, there were significant differences, favoring omalizumab. Overall, in the population with moderate-to-severe asthma, 4.5% had a serious adverse event with omalizumab, and 6.4% did so with placebo (odds ratio 0.72, 95% CI 0.57 to 0.91). Limiting only to longer-term studies (>52 weeks), the incidences were slightly lower, but still favored omalizumab, 3.7% vs. 6.7% (relative risk 0.55, 95% CI 0.37 to 0.82).[27] In children, these incidences were 5.2% and 6.5% and the difference was not significant (relative risk 0.91, 95% CI 0.58 to 1.42), likely due to fewer patients (smaller sample size).[28] Our confidence in these findings is low to moderate.

 Two observational studies have evaluated serious harms associated with omalizumab, including a prospective cohort study[23-25] and an analysis of adverse event reports submitted to the FDA.[26] The fair-quality EXCELS study was a prospective cohort study (N=5041) conducted between 2006 and 2011, and was funded by Genentech and Novartis. Patients with moderate-to-severe allergic asthma were followed for up to 5 years, with a mean of 3.7 for omalizumab and 3.5 for the control group ("no omalizumab"). The study also reported other outcomes that are not eligible for inclusion in this review. A 2014 publication reported on malignancies that occurred during the course of the study, finding crude rates of 16.0 per 1000 patient-years with omalizumab and 19.1 with placebo, with no statistical difference based on unadjusted analysis.[24] The crude (unadjusted for potential confounders) rate ratio was not statistically significant (0.84, 95% CI 0.62 to 1.13). A time-to-event analysis found no statistically significant difference between groups (hazard ratio 1.09, 95% CI 0.87 to 1.38). Analyses excluding non-melanoma skin cancers found similar results, as did subgroup analyses excluding patients with pre-existing malignancy, a history of malignancy, and a history of prior use of omalizumab. In a letter to the editor, Li et al. noted (1) the inclusion of prevalent users, (2) the small proportion of patients with a history of cancer or premalignant conditions, and (3) losses to follow-up as concerns about these analyses.[30] While the study was fair quality overall, these multiple concerns suggest caution in interpreting the findings. Overall this evidence is insufficient to draw conclusions.

 In a second analysis from the EXCELS study, cardiovascular and cerebrovascular events were evaluated, in particular arterial thromboembolic events (ATEs). Similar to the malignancy analysis, most events were reported only as crude incidence rates. The incidence of any cardiovascular or cerebrovascular event was 13.4 per 1000 patient-years with omalizumab, compared with 8.1 for the control group. Within the individual events reported, myocardial infarction and unstable angina had the largest difference between groups. The analysis of ATEs reported as serious adverse events during the study found a non-significant increase (adjusted hazard ratio 1.32, 95% CI 0.91 to 1.91).[23] Related to this analysis is an earlier publication of an analysis of ATEs reported to the FDA Adverse Event Reporting System (AERS).[26] All reports of ATEs submitted between 2004 and 2011 were analyzed (N=293,783). Compared with reports on

non-asthma drugs, omalizumab had a significantly increased risk (odds ratio 2.75, 95% CI 2.39 to 3.16). Inhaled corticosteroids had an even greater risk of reporting ATEs (odds ratio greater than 6), and all other classes or combinations of asthma drugs had no increased risk. However, the analysis of reports of ATEs for omalizumab versus all drugs, including other asthma drugs, found a lower, non-significant risk (odds ratio 1.09, 95% CI 0.95 to 1.24). Overall this evidence is insufficient to draw conclusions.

Withdrawal due to Adverse Events
Withdrawals due to adverse events were few, with no clear differences between groups.[16,28]

Secondary Outcomes

Change in Use of Inhaled Corticosteroids
The Cochrane review analysis of 4 RCTs (N=529) found that 42% of patients treated with omalizumab were able to completely discontinue inhaled corticosteroids, compared with 21% on placebo (odds ratio 2.50, 95% CI 2.00 to 3.13).[16] Similarly, the proportion of patients able to reduce the dose of inhaled steroid by 50% or more was significantly greater with omalizumab than placebo (77% versus 56%, 4 RCTs, odds ratio 2.50, 95% CI 2.02 to 3.10), and the mean difference in dose reduction was -141.24 mcg (beclomethasone dipropionate equivalents) (95% CI -221 to -61, based on 3 RCTs, N=1188). In the single study of children reporting this outcome, the median dose reduction was 100% with omalizumab and 66.7% with placebo (P=0.001).[31]

Change in Use of Oral Corticosteroids
A single small RCT (N=95) reported on withdrawal of oral corticosteroids, with no significant effect of omalizumab (odds ratio 1.18, 95% CI 0.53 to 2.63).[32] Similarly, there was no difference in dose reduction.

Change in Use of Rescue Medication
Based on 9 RCTs, omalizumab treatment resulted in a small, but significant reduction in the use of rescue medication (inhaled short-acting beta-agonists) (mean difference in puffs per day -0.39, 95% CI -0.55 to -0.24).[16]

Hospitalizations (all-cause)
Based on 4 RCTs, omalizumab resulted in a reduction in hospitalizations over 28 to 60 weeks of treatment (0.5% with omalizumab, 3% with placebo, odds ratio 0.16, 95% CI 0.06 to 0.42).[16]

Symptom Change
The Cochrane review reported that symptoms were significantly improved with omalizumab compared with placebo in only 6 of 11 RCTs reporting on symptoms, with the absolute differences being small.[16] However, due to the variation in methods for ascertaining and reporting on symptoms, pooling was not undertaken.

Global Assessments
Patient assessment of asthma control was better with omalizumab than with placebo in patients with moderate-to-severe asthma concurrently using a corticosteroid (4 RCTs, odds ratio 2.12, 95% CI 1.67 to 2.68).[16] The Cochrane review authors note caution in interpreting these findings due to significant heterogeneity (I^2=69%). Subgroup analyses found that the effect was larger in

patients with moderate-to-severe asthma (odds ratio 3.32, 95% CI 2.19 to 5.05) than in patients with severe asthma (odds ratio 1.69, 95% CI 1.26 to 2.26).

Injection Site Reactions

Based on 9 RCTs (N=3577), significantly more patients experienced injection site reactions with omalizumab than placebo (6% versus 9%, odds ratio 1.72, 95% CI 1.33 to 2.24).[16]

Off-Label Asthma Populations

Through our searches, we also identified 3 small trials of omalizumab in patients with asthma that did not fit our criteria because they were not populations included in the current product label. These were patients with non-atopic (non-allergic) asthma (2 RCTs, N=59),[33,34] and patients with both nasal polyps and asthma (1 RCT, N=24).[35] These exploratory studies of off-label uses of omalizumab are discussed only narratively here.

Two small RCTs (N=59, 16 and 20 weeks in duration) evaluated the effect of omalizumab in patients with non-atopic (non-allergic) asthma.[33,34] Both studies found reductions in intermediate outcomes related to IgE, and significantly improved lung function. Other measures also improved, but did not reach statistical significance. In the larger study (N=41), exacerbations and physician's global impression were numerically better with omalizumab at 16 weeks.[33] In the smaller study (N=18), background treatments were reduced over the final 6 to 8 weeks of the study.[34] The patient's assessment of asthma control was better with omalizumab, but quality of life scores were similar.

A third small trial (N=24) evaluated omalizumab given for 16 weeks to patients with nasal polyps and comorbid asthma (mixed group of allergic and non-allergic).[35] Nasal polyps were reduced significantly compared with placebo (-2.67, P=0.001). Symptoms improved with omalizumab but lung function and quality of life did not show clear improvements compared with placebo.

Chronic Spontaneous Urticaria

We identified 1 good-quality systematic review of 7 RCTs (N=1312) and 2 RCTs (N=248) of omalizumab in patients with chronic spontaneous urticaria.[36-38] One of the newer trials was rated poor quality for numerous reasons,[37] and the other, conducted in Korean and Japanese patients, (N=218) was good quality. Omalizumab was dosed at 75 to 600 mg every 2 to 4 weeks; patients included both adults and children, and were refractory to typical treatments for CSU (primarily antihistamines).

Key Outcomes for this Review

Complete Response

All of the included studies reported complete response, defined as Urticaria Assessment Scale UAS7 score scale of 0.[36,38] In the review of 7 RCTs, 28% of omalizumab patients achieved complete response, versus 6% with placebo (relative risk 4.55, 95% CI 3.33 to 6.23).[38] In the newer RCT of Japanese and Korean patients the effect with 300 mg was larger than the effect with 150 mg.[36] With 300 mg the rates were 35.6% versus 4.1% (odds ratio 15.30, 95% CI 4.27 to 54.90), and 150 mg they were 18.6% versus 4.1% (odds ratio 5.36, 95% CI 1.43 to 20.08).[36] Our confidence in these findings is high – future studies are very unlikely to change the direction or general magnitude of effect.

Quality of Life

Quality of life was not reported in the systematic review, but in the RCT of Japanese and Korean patients, quality of life in both groups of omalizumab, as measured by the Dermatology Life Quality Index (DLQI), improved more with omalizumab than with placebo.[39] The change from baseline (least mean squares) for omalizumab 300 mg, 150 mg, and placebo were -8.4, -7.2, and -5.3 and the differences between drug and placebo were -3.1 (95% CI -4.59 to -1.69) for 300 mg omalizumab and -1.9 (94% CI -3.36 to -0.44) for 150 mg omalizumab.

Serious Adverse Events and Withdrawals due to Adverse Events

In the newer RCT, adverse events were infrequent and there were no differences between groups on serious adverse events (4.1% vs. 4.2% vs. 0%, EPC calculated P-value=0.19) or withdrawals due to adverse events (0% vs. 1.4% vs. 0%).[36]

Secondary Outcomes

Pruritus

In the RCT of Korean and Japanese patients, omalizumab significantly improved the weekly itch severity score (ISS7) at 12 weeks (mean change -10.22, -8.80, and -6.51 for omalizumab 300 mg, 150 mg, and placebo; P<0.001 and P=0.006).[36]

Other Indications (off-label)

A very small RCT of patients with severe refractory atopic dermatitis (N=8, mean age 11.6 years) evaluated omalizumab or placebo given every 2 to 4 weeks for 24 weeks.[40] Randomization did not result in balanced groups in terms of age; the omalizumab group was a mean of 7.4 years, compared with 15.8 years in the placebo group. While numerous intermediate measures were reported to have improved, the Scoring Atopic Dermatitis scale (SCORAD) improved in both groups. No serious adverse events were reported.

Conclusions

The body of evidence consisted of 19 RCTs, 4 systematic reviews (of 30 RCTs), and 2 observational studies that were mostly fair to good quality. In patients with severe asthma, with elevated eosinophils, there was high-strength evidence that IL-5 inhibitors benralizumab and mepolizumab reduce the incidence of asthma exacerbations requiring oral corticosteroids or an emergency department visit or hospitalization. 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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