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Does dupilumab decrease the amount of asthma exacerbations in patients suffering from asthma compared to placebo?

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ABSTRACT

OBJECTIVE: The objective of this systematic EBM review is to determine "Does dupilumab decrease the amount of asthma exacerbations in patients suffering from asthma compared to placebo?"

STUDY DESIGN: A review of three randomized, placebo-controlled trials (RCTs) that were peer reviewed and published in English after 2009.

DATA SOURCE: All articles were published in peer reviewed journals and were researched using PubMed. Studies were selected based on their ability to answer the question posed in the objective, and if the researched outcomes were patient oriented.

OUTCOMES: Assessed outcomes were either the occurrence or rate of asthma exacerbations during the studies. The specifics of a defined exacerbation were similar, but minimally different between each randomized controlled trial. Exacerbations according to the authors are as follows:

i. Wenzel (2013): ">1 systemic glucocorticoid burst, in patient hospitalization, or an emergency department visit for worsening asthma"
ii. Wenzel (2016): "deterioration of asthma that required the use of systemic corticosteroids for at least 3 days, or hospital admission or emergency department visit because of asthma treated with systemic corticosteroids"
iii. Rabe: "events leading to hospitalization, and ED visit, or treatment of >3days with systemic glucocorticoids at >2 times the current"

RESULTS: All three studies found that Dupilumab had a large treatment effect on patients with asthma and decreased exacerbations. Wenzel et al. (2013) found a NNT of three, with an odds ratio (OR) of 0.08 (95% CI, 0.02 to 0.28, $p<0.001$) in favor of intervention decreasing risk for exacerbation. Wenzel et al. (2016) had a NNT of seven, with a risk reduction percentage of 70.5% (95% CI, 45.4-84.1%, pvalue=0.0001) with Dupilumab intervention. And Rabe et al. found an RR of 0.407 (95% CI, 0.263 to 0.630) meaning there is less than half the risk of an exacerbation with intervention.

CONCLUSIONS: The results of these three studies showed that Dupilumab does decrease the amount of asthma exacerbations compared to placebo in patients suffering from asthma. However, further research with more patients needs to be conducted with more consistent treatment protocols to understand optimal dosing.

KEYWORDS: Dupilumab, asthma

INTRODUCTION:

Asthma is a chronic disease with genetic predisposition that is characterized by varying levels of airway obstruction, inflammation and hyperresponsiveness. Symptoms can be both episodic or chronic, but are considered to be reversible either spontaneously or post-bronchodilator therapy as reported by an increase of ≥12% in $FEV_{1.}$[1] The reversibility of obstruction using a bronchodilator is what separates asthma from other obstructive lung diseases such as chronic bronchitis or emphysema. Patients with persistent, moderate-severe asthma who are uncontrolled may be having daily symptoms of wheezing, coughing and dyspnea despite treatment with inhaled corticosteroids (ICS), long acting beta agonists (LABA) and rescue inhalers putting them at a greater risk for exacerbations and hospital admission.[1,2]

Asthma is a common chronic disease amongst all age groups that effects healthcare providers in many different settings. The incidence of asthma accounts for 24.6 million Americans[3], and more than 250 million people affected worldwide.[2] Asthma patients account for 8-10% of the population[1], and 20-25% of those diagnosed are considered to have moderate to severe uncontrolled disease. Uncontrolled asthma, meaning that a patient still experiences symptoms and exacerbations despite the use of maintenance medications such as ICS and some other controller or systemic corticosteroids.[2]

With the increasing prevalence of asthma over the past 20 years, there is both a large economic and resource burden placed on healthcare systems worldwide. In the United States alone, there are some 10 million hospital visits and 1.8 million emergency room visits each year as a result of asthma. These emergency room visits ultimately result in more than 3,500 deaths in the US, most commonly amongst young blacks between the ages of 15 and 24.[1] As a result, in

2013 about $50.3 billion was spent in the US on medical costs for asthma alone, not including the $29 billion from asthma-related mortality.[4]

Usual treatment methods depend largely on the severity and frequency of a patient's symptoms and are often approached with a stepwise treatment plan. This includes starting with a short acting beta agonist such as albuterol for quick relief in addition to a maintenance ICS of varying dosages such as budesonide or fluticasone for those with persistent asthma. LABAs such as salmeterol are often added on for patients already on ICS with poor control, in addition to other adjunct medications such as leukotriene receptor antagonists montelukast or zafirlukast.[1] Biologic medications are being explored further as adjuncts for the treatment of uncontrolled asthma. Omalizumab has been found to be helpful in patients with a positive skin test due to its effect on the inhibition of IgE binding which has a key role in allergic asthma symptoms.[1,2] Other biologics such as reslizumab and mepolizumab affect interleukin5, and have been found effective in patients with elevated eosinophilic asthma. With poor asthma control, patients are placed at a greater risk of a life-threatening exacerbation and a decreased quality of life. Symptoms of breathlessness, inability to complete full sentences and a sensation of chest tightness are common complaints during an asthma exacerbation. Exacerbations are treated with a combination of supplemental oxygen, inhaled SABA via nebulizer or metered dose inhaler (MDI) treatment, and oral systemic corticosteroids contributing to immunosuppression.

The mechanisms associated with poor asthma control in those who are using ICS and LABAs is not fully understood.[3] More recent research has come to find that about half of patients with asthma have inflammatory cytokines attributed to type 2/Th2 inflammation, and new therapies are being tested to reduce this specifically to improve control.[2]

Dupilumab (Dupixent®) has shown success and improvement with other type 2 inflammatory disease processes such as atopic dermatitis and chronic sinusitis, common comorbidities of asthma.[2] This information is making researchers hopeful that Dupilumab, a fully human monoclonal antibody, will be helpful in asthma control therapy through the inhibition of interleukins-4 and 13 involved in Th2 inflammatory pathways.[2] Dupilumab may be used as an add-on controller medication to decrease the amount of severe exacerbations experienced by asthma patients, especially those with moderate to severe asthma. This paper evaluates three randomized placebo-controlled trials comparing the efficacy and safety of anti-interleuken-4 receptor monoclonal antibody Dupilumab in the treatment of persistent asthma and its prevention of asthma exacerbations.

OBJECTIVE:

The objective of this systematic EBM review is to determine "Does Dupilumab decrease the amount of asthma exacerbations in patients suffering from asthma compared to placebo?"

METHODS:

Resources and scholarly literature were selected by the author of this paper based on their ability to answer the question: Does Dupilumab decrease the amount of asthma exacerbations in patients suffering from asthma compared to placebo? The articles were also selected because they discuss a new intervention being proposed for better asthma control that includes a patient oriented outcome (POEM), in this case decreased occurrence of an exacerbation. All articles were published in peer-reviewed journals in English, with exclusion criteria including articles that were published before 2009. All three of the studies included are double-blind, randomized, placebo-controlled clinical trials published in years 2013, 2016 and 2018 found using the key words "Dupilumab" and "asthma" through the resource database Pubmed. Inclusion criteria

Table 1. Demographics and Characteristics of Included Studies

Study	Type	# Patients	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Wenzel 2013	Double blind RCT	104	Adults 18 to 65 years of age	Patients 18-65 y/o, w/ persistent moderate-severe asthma, ≥300 blood eosinophil count, and poorly controlled with medium-high dose ICS; ≥1 exacerbation within 2 years.	Patients outside of the age range, and those with low eosinophil counts; ACQ5 score outside of 1.5-3.0	24	300mg SQ Dupilumab every week vs. placebo while discontinuing their LABA at week 4, and decreasing ICS dose during weeks 6-9.
Wenzel 2016	Double blind RCT	471	Adults ≥18 years old	Adults ≥18 y/o with a diagnosis of asthma ≥12 months, with medium-high dosed ICS plus a LABA; FEV_1 of 40-80% and ACQ5 score ≥1.5 at screening; ≥1 exacerbation within 1 year.	Diagnosis of COPD or other lung disease, use of PO steroids within 28 days of screening, current smokers, or those who quit within 6 months.	34	300mg SQ dupilumab q 2 or 4 weeks following the 600mg loading dose at week one vs. placebo
Rabe 2018	Double blind RCT	210	Patients ≥12 years of age	Patients ≥12 y/o, with physician diagnosed asthma x1yr, receiving treatment w/ regular PO glucocorticoids, and high dose ICS w/ a second controller; FEV_1 before bronchodilator use of ≤80%	Patients <12 y/o, under 30 kg, and those with other COPD or lung diseases; current smokers, or those with URI or ER treatment within 4 weeks of visit 1	7	300mg SQ Dupilumab post 600mg loading dose q 2 weeks vs. matched placebo. During weeks 4-20, steroid doses were decreased q4wks

included studies that were randomized controlled trails, and those published within the past 10 years. Statistics reported and used include OR, RR, NNT and p-values.

The selected studies, as detailed above in Table 1, include a population of patients diagnosed with asthma, who were given the intervention of 300mg Dupilumab, at either weekly or every two week frequencies depending on the study. Changes to patients' previous asthma control medications throughout each study slightly varied. The patients that were given the intervention were all compared to an experimental group who received a similar appearing placebo and the measured outcome was the occurrence or rate of asthma exacerbations.

OUTCOMES:

Outcomes were measured by the occurrence of a severe exacerbation in both Wenzel studies, and as a rate of severe asthma exacerbations in Rabe 2018 study. The definitions of an exacerbation were similar, but minimally different between studies.

I. Wenzel (2013): "≥1 systemic glucocorticoid burst, in patient hospitalization, or an emergency department visit for worsening asthma".[3]
II. Wenzel (2016): "deterioration of asthma that required the use of systemic corticosteroids for at least 3 days, or hospital admission or emergency department visit because of asthma treated with systemic corticosteroids".[2]
III. Rabe: "events leading to hospitalization, and ED visit, or treatment of ≥3days with systemic glucocorticoids at ≥2 times the current".[5]

RESULTS:

Wenzel et al. (2013) study was a randomized placebo-controlled trial that took place in 28 different sites throughout the US. Patients were required to have an elevated eosinophil count (≥300 cells/μL) in addition to diagnosis of moderate to severe asthma not properly controlled

with medium to high dose ICS and a LABA inhaler before the start of the trial. All patients were between the ages of 18 and 65, with uncontrolled symptoms. A ratio of 1:1 was used to randomize via a "centralized system" to achieve randomization allocation concealment.[3] Patients in the intervention group were given 300mg Dupilumab or placebo every week. Unique to this study, patients were required to taper their maintenance medications such that they discontinued their LABA at week four, and then continued to taper their ICS so that they would discontinue by weeks six through nine of the total 12-week intervention period. This particular study looked at the occurrence of an asthma exacerbation during the 12-week intervention as their primary outcome, and patients continued to receive the study drug all 12 weeks or until they had an exacerbation. Of those receiving Dupilumab, 6% had an exacerbation compared to 44% in the placebo group (Table 2).[3] The study reports an OR far below one, at 0.08 (95% CI, 0.02 to 0.28; $p<0.001$) with Dupilumab, indicating that the intervention decreased the risk for asthma exacerbation in this study in patients that were given the intervention compared to placebo.[3] Given dichotomous data from the researchers, a NNT of 3 was calculated indicating that for every three moderate to severe persistent asthmatics treated with Dupilumab, one more asthma exacerbation will be prevented compared to the placebo. A low NNT and an OR significantly smaller than one with a narrow CI, indicates a large treatment effect that is statistically significant based on the reported p-value. It is important to note that although more than 20% of the placebo group discontinued the study, it was due to a "lack of efficacy", considering that the patients had to discontinue their LABA and ICS. This means that patients were possibly receiving no medication for their asthma control if given the placebo at the time of their exacerbation.[3]

Table 2. Occurrence of Asthma Exacerbation in Wenzel et al. 2013 Study

Intervention	Occurrence of asthma exacerbation during 12 wk intervention
Dupilumab (n=52)	3 (6%)
Placebo (n=52)	23 (44%)

Wenzel et al. 2016 is a randomized placebo-controlled clinical trial that took place in 174 sites across 16 different countries. Patients in this 2016 trial had similar inclusion criteria such as being ≥18 years old, with an asthma diagnosis for ≥12 months and those uncontrolled on medium to high-dose ICS and a LABA inhaler. The main difference in patient population in this study was that patients were selected irrespective of their blood eosinophil counts, including those with greater than and less than 300 cells/μL.[2] Results were reported for both the overall population, and in the different subgroups based on eosinophil count. Reference exclusion criteria in Table 1. With a total of 769 patients, there were four different intervention groups with 150-157 patients each, and a placebo group with 158. Randomization was achieved via a centralized allocation system. Different interventions included receiving Dupilumab subcutaneous (SQ) 200mg every two or four weeks, and 300mg every two or four weeks.[2] All intervention groups received a loading dose double that of their normal dose for the first injection. More than 89% of patients completed the study (689/769 total patients).[2]

For this review, results regarding the 300mg SQ injection every two weeks were utilized for calculation purposes and conclusions in this report. Amongst patients who received this intervention, a statistically significant risk reduction percentage of 70.5% (95% CI, 45.4-84.1%, p value=0.0001) was found when compared to placebo. Of those receiving Dupilumab 300mg every two weeks, 11% suffered from an exacerbation compared to 26% in the placebo intervention.[2] Because this information was reported as dichotomous data within the study, NNT of 7 was calculated indicating another large treatment effect. For every seven adults with

uncontrolled persistent asthma treated with Dupilumab 300mg every two weeks, one more person will have an asthma exacerbation prevented compared to placebo.

Table 3. Calculations for NNT in Both Wenzel et al. Studies

Study	EER	CER	RRR	ARR	NNT
Wenzel 2013	0.94	0.56	0.67	0.38	**3**
Wenzel 2016	0.89	0.74	0.20	0.15	**7**

The final study, by Rabe et al., was a randomized, placebo-controlled international study that included 210 patients. Inclusion criteria in this study was slightly different and included patients ≥12 years old, with an asthma diagnosis ≥ 12 months with oral glucocorticoid dependent severe asthma who were receiving systemic steroids within the six months preceding the study in addition to a high dose ICS and up to two other inhalers. Review Table 1 for exclusion criteria. Researchers allowed a three to 10 week adjustment period for the patient's oral glucocorticoids before beginning the 24 week intervention. Patients were either given 300mg SQ Dupilumab with an initial loading dose of 600mg every two weeks, or matched placebo. Oral steroid doses were reduced and adjusted during weeks four through 20.[5] Randomization to receive placebo or intervention was achieved via a "voice web response technology."[5]

The rate of a severe exacerbation was recorded by the researchers, but this could not be converted to dichotomous data for a NNT calculation. The study did however find a relative risk versus placebo of 0.407 (95% CI, 0.263 to 0.630) meaning that there is less than half the risk of an exacerbation with 300mg Dupilumab every two weeks compared to placebo.[5] There is no reported p-value. Although the treatment effect is also large, the existence of a wider confidence interval makes the data found less precise, meaning that results in other studies may show dissimilar results. However, there is not large concern that the intervention would increase the risk of these patients' exacerbations given that the CI does not exceed one. Loss of subjects who did not complete the entire intervention was less than 20%.

Among all three studies, the most common adverse event included an injection site reaction and erythema, with other common events such as upper respiratory tract infection or headache. Treatment was tolerable for patients in all studies. Notable to mention, in the study done by Wenzel et al. 2016, there were two patient deaths, although they were in the intervention group with Dupilumab 300mg *every four weeks*, not every two weeks. According to the authors, the deaths were unrelated to treatment as one patient passed from acute heart failure and the other from metastatic gastric cancer with complications of pneumonia and cor pulmonale.[2] No deaths were recorded in either of the two other studies.

Table 4. Most Common Adverse Events in All Studies

Study		Injection site reaction	Upper resp. Infection	Headache
Wenzel 2013	Dupilumab (n=52)	15 (29%)	7 (13%)	6 (12%)
	Placebo (n=52)	5 (10%)	9 (17%)	3 (6%)
Wenzel 2016	Dupilumab (n=156)	33 (21%)	20 (13%)	17 (11%)
	Placebo (n=158)	12 (8%)	28 (18%)	20 (13%)
Rabe 2018	Dupilumab (n=103)	9 (9%)	9 (9%)	Not reported
	Placebo (n=107)	4 (4%)	19 (18%)	Not reported

DISCUSSION:

Previous clinical trials researching antibody treatment options for Th2 inflammatory diseases have shown consistent positive results in patients with elevated eosinophil counts, explaining why Wenzel et al. 2013 initially only included patients with blood eosinophil counts ≥300 cells/μL.[3] Interestingly enough, future studies including the other two analyzed in this review have found that Dupilumab was successful in decreasing exacerbation risk and improving lung function in asthma patients regardless of their baseline blood eosinophil count.[2,5]

There are other labeled uses for Dupilumab including moderate to severe atopic dermatitis and chronic rhinosinusitis with nasal polyposis that were successful before using it in trials as an adjunct asthma medication. Similar to when treating asthma, some of the most

common adverse reactions found were injection site reactions.[6] In studies specifically involving patients with atopic dermatitis, severe eye irritation in addition to blepharitis, conjunctivitis and keratitis were recorded as adverse effects not reported in asthma trials.[7] The only contraindication for Dupilumab found is a known hypersensitivity to the drug or any of its components and there are currently no black box warnings.[6,7] However, Dupilumab is known to have drug interactions with live vaccines and simultaneous injections should thus be avoided if possible. Patients who are using Dupilumab for atopic dermatitis are advised to continue taking their asthma medications as directed unless otherwise advised by their healthcare provider to prevent unnecessary exacerbations.[6] Due to the successful treatment of several comorbid conditions, it is possible that this one drug will be able to treat all conditions systemically at once.[2]

Research on this topic was limited in the author's search given that only PubMed was used to find studies that answered the question: "Does Dupilumab decrease the amount of asthma exacerbations in patients suffering from asthma compared to placebo?". It is possible that there are more, and better studies to be found on other databases. Limitations of the studies themselves include relatively small sample size and short duration of treatment. In addition to that, the methodology of each study was slightly different in how they altered their patients' previous medications making direct comparison more difficult. For example, in Wenzel et al. 2013 study, patients were changing their maintenance medication at weeks four, six, and nine giving them little time to adjust to each dose[3]. In the Rabe et al. study, the only medication that changed was their oral corticosteroids, but these patients maintained their inhalers throughout the whole study[5]. In addition to this, none of the studies included a "worst-case" analysis on patients lost to follow-up. Both Wetzel et al. studies excluded missed data from their analysis, and Rabe et al.

used a mixed model. It would increase validity to find risk reductions and a low NNT despite the fact that all patients who left the study were counted towards exacerbation rates or counts in their respective studies. A final limitation notable to mention found in the study by Rabe et al., is that because the annualized rate of severe exacerbations reported was not the primary endpoint of their study, it was not "controlled for comparison" and thus only reported a confidence interval, but no p-value for complete statistical significance.[5]

CONCLUSION:

According to the results reported in this systemic review, Dupilumab does decrease the amount of asthma exacerbations in patients diagnosed with asthma compared to placebo. Statistically significant, large treatment effects were found in both studies published by Wetzel et al. with small NNT of 3 and 7, and a significant risk reduction percentage with Dupilumab at 95% confidence in study by Rabe et al. Further research however needs to be done to confirm the most ideal dose and administration schedule given that there were differences in that regard amongst studies. Future research would be most beneficial if they included larger sample sizes, and monitored treatment effects and adverse events for a longer period of time for increased confidence in Dupilumab treatment of uncontrolled asthma. Data analysis could also be incorporated to look at patients specifically with comorbid asthma and atopic dermatitis or chronic sinusitis to monitor improvement of all conditions at the same time to see if there is increased effect on one condition over another. And finally, patient population may also be expanded to include children six and older, as use is approved in this age group for the treatment of severe atopic dermatitis.[6] Although other current ongoing studies with Dupilumab were not found in my research, new treatment options for patients with uncontrolled asthma will continue to benefit and one day improve the lives of millions affected by this common disease.

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