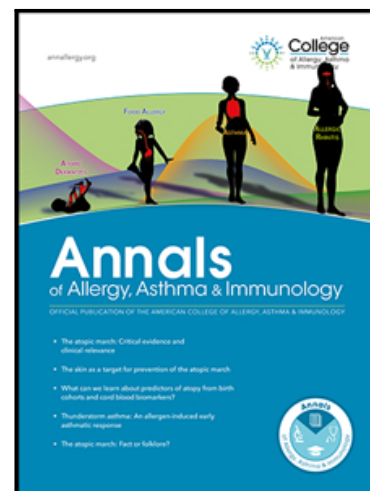


Real-world efficacy and safety of Dupilumab use in the treatment of asthma

Somaira Nowsheen MD PhD , Jared I Darveaux MD

PII: S1081-1206(21)00274-X
DOI: <https://doi.org/10.1016/j.anai.2021.04.011>
Reference: ANAI 3564



To appear in: *Annals of Allergy, Asthma Immunology*

Received date: 11 February 2021
Revised date: 1 April 2021
Accepted date: 8 April 2021

Please cite this article as: Somaira Nowsheen MD PhD , Jared I Darveaux MD , Real-world efficacy and safety of Dupilumab use in the treatment of asthma, *Annals of Allergy, Asthma Immunology* (2021), doi: <https://doi.org/10.1016/j.anai.2021.04.011>

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Title: Real-world efficacy and safety of Dupilumab use in the treatment of asthma

Authors: Somaira Nowsheen¹, MD PhD, Jared I Darveaux², MD

Affiliations: ¹Gundersen Lutheran Medical Foundation, La Crosse, WI, USA;

snowshee@gundersenhealth.org; ²Department of Allergy Immunology, Gundersen Health System, Onalaska, WI, USA; jidarvea@gundersenhealth.org.

Correspondence: Jared I Darveaux, MD, Department of Allergy Immunology, Gundersen Health System, 3111 Gundersen Drive, Onalaska, WI 54650, USA, Office Phone: (608) 775-3400, Fax: (608) 775-4555, email: jidarvea@gundersenhealth.org

Word count text: 994

Short title: Dupilumab and asthma

Figures and Tables: 1

Number of references: 7

Conflict of interest: JID serves on the speaker's bureau for Sanofi/Regeneron, GSK and AstraZeneca and has received honoraria for those services. SN has no conflict of interest to disclose.

Funding Sources: None

The study was approved by Gundersen Lutheran Institutional Review Board.

This work has not been previously presented and is not under consideration for publication elsewhere.

Reprints may be requested by contacting the address indicated above.

Keywords: Dupixent, dupilumab, asthma, steroid, immunotherapy, biologic, effectiveness

Abbreviations: ACT, asthma control test; F_eNO, fraction exhaled nitric oxide; L, liter; mo, month; n, number; SD, standard deviation

Asthma affects people of all races and ethnic groups worldwide¹. Uncontrolled asthma has a significant impact on daily life with unscheduled clinic or emergency room visits, hospitalizations, and impact on daily activity². Symptoms of asthma including cough, shortness of breath, chest tightness, and wheezing, have a significant impact on quality of life. Frequent exacerbations can lead to airway remodeling, worsening obstruction, and reduced lung function. Inhaled corticosteroids and beta agonists have been the treatment of choice for years. While many patients are well controlled with inhaled treatment options, many have uncontrolled symptoms and ongoing exacerbations. Those with frequent exacerbations are subjected to systemic corticosteroids which carry a risk of significant short- and long-term side effects. Recent development of biologic therapies has broadened treatment options, offering hope to those with difficult to control asthma. One of the newest biologic agents, dupilumab, is a human monoclonal antibody that inhibits signaling of interleukin-4 and interleukin-13. These Th2 cytokines drive inflammation in allergic diseases such as atopic dermatitis, asthma and nasal polyposis³. Dupilumab is approved for use as an add-on maintenance treatment for people 12 years old and over who have moderate-to-severe eosinophilic or oral steroid dependent asthma that is not controlled with their current asthma medicines^{4,5}. Studies on real-world safety and

efficacy of dupilumab on asthma treatment are lacking. Our aims were to determine the effectiveness and adverse effects of dupilumab in asthmatics.

An electronic search of our institution's medical records (January 1, 2017 to September 1, 2020) was performed to identify patients with clinical diagnoses of asthma who were treated with dupilumab. Inclusion criteria included: diagnosis of uncontrolled asthma by a pulmonologist or allergist, treatment with dupilumab for at least 1 dose, and at least one visit prior to and one visit after initiation of dupilumab. The health records were reviewed manually to extract the following: patient characteristics, spirometric measures, peripheral eosinophil counts at baseline and after treatment with dupilumab, fraction exhaled nitric oxide (F_eNO) before and after therapy, dupilumab treatment dose and duration, prior and concurrent therapies, asthma exacerbation frequency before and after treatment, response to treatment, and adverse effects. Clinically meaningful response, defined as one of the following: ACT score improvement from uncontrolled (<20) to a controlled score (≥ 20); F_eNO decrease from elevated levels (≥ 25 ppb) to normal (<25 ppb); improvement of ≥ 120 ml in FEV_1 , was noted for each patient on follow-up. Standard statistical analysis using GraphPad Prism was performed to analyze the data. All tests were two-sided with alpha level set at 0.05 for statistical significance.

72 patients with a median age of 49 years (range, 12 - 78 years) met study inclusion criteria.

Table 1 lists the study results. Patients received treatment with dupilumab for a median duration of 12 months (range, 1 - 36 months), and the median follow-up time was 13 months (range, 2 - 36 months). The median dose of dupilumab was 300 mg every 2 weeks (range, 200 - 300 mg).

While on dupilumab, 68 patients (94.4%) experienced subjective improvement of asthma. Approximately a 6-point increase in asthma control test (ACT) score, 181mL (6%) increase in FEV₁ percent predicted, and 24-point decrease in exhaled nitric oxide (F_eNO) was noted after dupilumab treatment. Eosinophil count decreased by 0.39×10^3 eosinophils/ μ L (normal range $0-0.5 \times 10^3$ eosinophils/ μ L) with dupilumab therapy. More importantly, 20 patients (27.8%) who had failed treatment with other biologics responded to dupilumab. Of the 9 patients on steroid therapy, 6 patients (66.7%) were able to discontinue daily oral steroids while 2 patients (22.2%) were able to decrease their daily dose. 3 patients stopped treatment due to adverse effects (**Table 1**).

Multiple medications are approved for prevention and treatment of asthma symptoms and exacerbations. Current guidelines recommend treatment with inhaled corticosteroids (ICS) either regularly or as needed in combination with formoterol for adults and adolescents over the age of 12. Indication for Dupilumab use includes moderate-to severe eosinophilic or oral steroid dependent asthma in those 12-years and older⁶. Based on our results, approximately 2 out of 3 patients see significant benefit with dupilumab treatment with minimal side effects. This is likely an underestimate since we used stringent clinical categories. Many patients had F_eNO, ACT score or FEV₁ values above our cutoff values to begin with and so were not deemed to have a clinically meaningful response with dupilumab.

In contrast to clinical trials where transient increases in peripheral eosinophils were seen, patients in our study were noted to have a decrease in their eosinophil count.⁷

Two patients in our cohort did not respond to dupilumab, though they did show initial improvement in their asthma symptoms. The reason for lack of response is unclear but may represent a distinct disease phenotype. Unfortunately, no clear predictors of failure were identified. Both patients were obese and had atopic dermatitis and allergic rhinitis. Patient 1 was a 73-year-old male with comorbid lichen simplex, nasal polyposis, hypertension and hyperlipidemia. Patient 2 was a 35-year-old female with obstructive sleep apnea and uncontrolled gastrointestinal reflux disease, a common contributor to uncontrolled asthma and the likely cause in this specific patient's case. She had failed multiple treatment approaches including other biologic medications. Given the success of this medication in those who qualify for treatment, to further hone precision medicine it may be prudent to focus future research on identification of likely non-responders.

One of the concerns with any treatment is adverse effects. In our experience, side effects were rare with dupilumab therapy.

Of note, many patients in our experience had to discontinue therapy or were unable to afford treatment due to cost, though their providers deemed them to be ideal candidates for dupilumab therapy. Limitations of access to biologic medications due to cost is a common hurdle that remains to be solved.

Taken together, our data demonstrate that real-world uncontrolled asthmatics experience significant improvement in symptoms, pulmonary function, markers of inflammation, and exacerbation frequency with dupilumab therapy. Dupilumab should be considered in appropriate patients as a treatment option to improve quality of life and reduce morbidity.

Table 1: Baseline demographics, characteristics, treatment regimen and outcomes of patients receiving Dupilumab for treatment of asthma (n=72)

	Characteristics	Value	p-value
Patient characteristics	Male (% , n)	40.3% (n=29)	
	Age (mean $\pm$ SD, years)	47.7 $\pm$ 17.5	
	BMI (mean $\pm$ SD)	31.2 $\pm$ 8.3	
	Caucasian (% , n)	93.1% (n=67)	
	Other ethnicity (% , n)	6.9% (n=5)	
	Current smoker ((% , n)	5.6% (n=4)	
	Former smoker (% , n)	23.6% (n=17)	
	Nonsmoker (% , n)	70.8% (n=51)	
Comorbidities	Allergic rhinitis (% , n)	80.6% (n=58)	
	Atopic dermatitis (% , n)	33.3% (n=24)	
	Nasal polyposis (% , n)	44.4% (n=32)	
Baseline Asthma characteristics	Childhood asthma onset (% , n) ^a	64.0% (n=34)	
	Adulthood asthma onset at age<50 (% , n) ^a	20.0% (n=10)	
	Adulthood asthma onset at age $\geq$ 50 (% , n) ^a	12.0% (n=6)	
	Moderate asthma (% , n)	38.9% (n=28)	
	Severe asthma (% , n)	61.1% (n=44)	
	Annual exacerbation frequency ^b (mean, n)	2.7	
	F _e NO (mean $\pm$ SD)	43.0 $\pm$ 39.9	
	ACT (mean $\pm$ SD)	16.0 $\pm$ 6.2	

	Eosinophil count (mean $\pm$ SD, eosinophils $\times 10^3$ per μL)	0.64 ± 0.47	
	Mean FEV ₁ (L)	2.6 ± 0.8	
	Mean FEV ₁ percent predicted (%)	80.6 ± 20.7	
Previous treatment	Aspirin desensitization (% , n)	8.3% (n=6)	
	Biologic therapy (% , n)	29.2% (n=21)	
	High-dose inhaled corticosteroids	100.0% (n=72)	
	Immunotherapy (% , n)	6.9% (n=5)	
	Leukotriene inhibitors (% , n)	73.6% (n=53)	
	Long-acting β_2 -agonist	95.8% (n=69)	
	Long-acting muscarinic antagonists (% , n)	11.1% (n=8)	
	Daily oral steroids (% , n)	12.5% (n=9)	
	Short-acting beta agonist (% , n)	86.1% (n=62)	
Dupilumab therapy ^c	Dupilumab dose, median (range), mg	300 (200- 300)	
	Duration of therapy (mean $\pm$ SD, mo)	12.3 ± 7.2	
	Follow up time (mean $\pm$ SD, mo)	14.5 ± 7.6	
Concurrent therapy ^d	High-dose inhaled corticosteroids	86.1% (n=62)	
	Immunotherapy (% , n)	4.2% (n=3)	
	Leukotriene inhibitors (% , n)	38.9% (n=28)	
	Long-acting β_2 -agonist	68.1% (n=49)	
	Long-acting muscarinic antagonists (% , n)	2.8% (n=2)	
	Daily oral steroids (% , n)	2.8% (n=2)	
	Short-acting beta agonist (% , n)	25.0% (n=18)	

Outcome	Clinically meaningful response ^e (% , n)	62.5% (n=45)	
	Any improvement in ACT score (% , n)	79.2% (n=57)	
	Any decrease in F _e NO (% , n)	76.4% (n=55)	
	Any improvement in FEV ₁ (% , n)	52.8% (n=38)	
	Discontinued or decreased dose of daily oral steroid (% , n)	88.9% (n=8)	
Asthma response	F _e NO (mean ± SD)	19.3 ± 15.5	p<0.05
	ACT (mean ± SD)	21.8 ± 4.5	p<0.05
	Eosinophil count (mean ± SD, eosinophils x 10 ³ per µL)	0.25 ± 0.23	p>0.05
	Mean FEV ₁ (L)	2.7 ± 0.9	p>0.05
	Mean FEV ₁ percent predicted (%)	86.6 ± 21.0	p>0.05
	Annual exacerbation frequency (mean, n)	0.1	p<0.05
Adverse effects	Experienced side effects ^f (% , n)	13.9% (n=10)	
Discontinued therapy	Discontinued therapy (% , n)	12.5% (n=9)	
	Discontinued due to side effects ^g (% , n)	4.2% (n=3)	
	Discontinued due to lack of response ^h (% , n)	2.8% (n=2)	
Associated response ^c	Complete response of concomitant atopic dermatitis	94.7% (n=18)	
	Complete response of concomitant nasal polyposis	92.9% (n=26)	
	Complete response of concomitant atopic dermatitis and nasal polyposis	100.0% (n=3)	

Abbreviations: ACT, asthma control test; F_eNO, fraction exhaled nitric oxide; L, liter; mo, month; n, number; SD, standard deviation

^a Data available for n=50

^b Defined as requiring systemic steroid use, hospitalization or adjunct therapy

^c Dupilumab was prescribed for additional indications in a subset of patients: asthma + atopic dermatitis (19 patients), asthma + nasal polyps (28 patients), asthma + atopic dermatitis + nasal polyps (3 patients)

^d Some medications were prescribed for other co-morbidities

^e Defined as one of the following: ACT score improvement from uncontrolled (<20) to a controlled score (≥20); F_eNO decrease from elevated levels (≥25 ppb) to normal (<25 ppb); improvement of ≥120 ml in FEV₁

^f Side effects included transient injection site reaction (n=4), conjunctivitis/ocular irritation/dry eyes (n=3), pain with injection (n=1), fatigue (n=1), severe hand and feet swelling, erythema and warmth and pruritus (n=1), lymphadenopathy (n=1)

^g Side effects included conjunctivitis, injection site reaction, lymphadenopathy

^h Both patients responded initially but then flared after 2 months of therapy

References

1. Fuseini H, Newcomb DC. Mechanisms Driving Gender Differences in Asthma. *Curr Allergy Asthma Rep.* 2017;17:19-19.
2. Zeiger RS, Schatz M, Dalal AA, et al. Utilization and costs of severe uncontrolled asthma in a managed-care setting. *The Journal of Allergy and Clinical Immunology: In Practice.* 2016;4:120-129. e123.
3. Simpson EL, Akinlade B, Ardeleanu M. Two Phase 3 Trials of Dupilumab versus Placebo in Atopic Dermatitis. *N Engl J Med.* 2017;376:1090-1091.
4. Castro M, Corren J, Pavord ID, et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. *New England Journal of Medicine.* 2018;378:2486-2496.
5. Rabe KF, Nair P, Brusselle G, et al. Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma. *New England Journal of Medicine.* 2018;378:2475-2485.
6. Grey A, Katelaris CH. Dupilumab in the treatment of asthma. *Immunotherapy.* 2019;11:859-872.
7. Castro M, Corren J, Pavord ID, et al. Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma. *New England Journal of Medicine.* 2018;378:2486-2496.