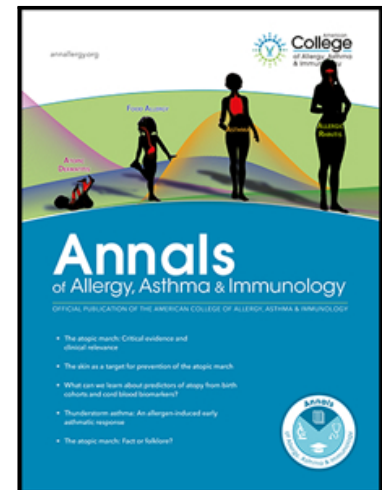


Dupilumab in the Treatment of Nasal Polyposis: A Retrospective, Real-world Study

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Title: Dupilumab in the Treatment of Nasal Polyposis: A Retrospective, Real-world Study

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Abbreviations: CT, computed tomography; mo, month; n, number; SD, standard deviation; %, percentage

Nasal polyposis is frequently associated with chronic rhinosinusitis, high symptom burden and poor quality of life. Options for treatment resistant disease include aspirin desensitization, recurring systemic corticosteroid use and sinus surgery.¹ Dupilumab is a human monoclonal antibody that blocks signaling of interleukin-4 and interleukin-13. These cytokines drive allergic diseases such as atopic dermatitis, asthma and nasal polyposis, for which dupilumab is an approved therapy.² In this retrospective cohort study, our aims were to assess real world efficacy and safety of dupilumab for treatment of nasal polyposis.

Upon receiving approval from our facility's Institutional Review Board, 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 nasal polyposis who were treated with dupilumab. Inclusion criteria included: diagnosis of nasal polyposis by an otolaryngologist 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 patient characteristics, treatment dose, treatment duration, concurrent therapies, response to treatment and adverse effects. Each patient's response to therapy was retrospectively graded based on the treating physician's impressions on follow-up as complete response, no response, or partial response. Clinically meaningful response was defined as change in polyp size with treatment as assessed using CT imaging or rhinoscopy, was noted for each patient on follow-up.

29 patients with a median age of 51.2 years (range, 24 - 73 years) met study inclusion criteria.

Table 1 lists the study results. Patients received treatment with dupilumab for a median duration of 12 months (range, 0 - 20 months), and the mean follow-up time was 11 months (range, 3 - 20 months). The dose of dupilumab was 300 mg every 2 weeks. While on dupilumab, 27 patients (93.1%) experienced improvement of nasal polyps and associated symptoms including congestion, anosmia and/or ageusia/hypogeusia. 24 patients (82.8%) reported complete response, and 3 patients (10.3%) reported partial response. 2 patients (6.9%) reported no response. 96.6% of patients (n=28) had objective response based on imaging or rhinoscopy. Based on CT imaging or rhinoscopy, 24 patients (82.8%) had complete response (no polyp noted) with dupilumab therapy while 5 patients (17.2%) had persistent polyps. Of them, 80% (n=4) had decrease in polyp size with dupilumab treatment, but not complete resolution. 76.9% of patients (n=10 out of 13) were able to discontinue systemic steroid use. One patient who was previously prescribed omalizumab for asthma continued to have uncontrolled nasal polyp symptoms. He was switched to dupilumab to better control nasal polyposis with subsequent improvement in symptoms.

As opposed to surgery and systemic steroid therapy, dupilumab has limited adverse effects and is well tolerated in our experience with excellent response.

No patients required surgical intervention after starting dupilumab. In addition, there was no significant benefit observed in those who had previously underwent polypectomy; 84.6% of patients with prior polypectomy experienced complete resolution of symptoms with dupilumab while the response rate was 81.3% in those without prior surgical intervention. Many patients with concurrent asthma saw improvement in their symptoms with dupilumab as well. In fact, 92% of patients with concomitant asthma saw improvement with dupilumab therapy.

Though most patients showed a significant response to dupilumab, two patients in our cohort did not. One had an adverse drug reaction of diffuse rash covering >50% body surface area and stopped treatment prematurely. Instead, he received triamcinolone injection and intranasal fluticasone. He was considering another trial of dupilumab at his last visit. The other patient continued dupilumab since her asthma was responsive to the medication. She received intranasal fluticasone and pseudoephedrine for nasal polyps at the time of last follow up.

Interestingly, conjunctivitis and other injection site reactions reported in the literature were not observed in our patient cohort, suggesting that there may be an association between the disease pathology and adverse effects.³

Besides dupilumab, omalizumab is approved for treatment of nasal polyps in the United States. One patient previously treated with omalizumab for asthma was switched to dupilumab for nasal polyposis with good response. Further studies are warranted to compare the response of nasal polyposis to these medications.

Due to the overwhelming response in our cohort, it is difficult to ascertain predictors of treatment response. Appropriate treatment duration has also not been established. Unfortunately, dupilumab is preventative and not curative meaning patients experience symptomatic benefit while on the medication, but their disease may recur once therapy is discontinued.

Limitations of this study include the small cohort size, retrospective design, and observer bias. In addition, due to the retrospective nature of the study, the results may have been subject to observer bias on the part of both patients and providers involved in this study. Participants received open label product, were not blinded, and there were no placebo control comparators, as is the case with most retrospective studies.

Given the excellent and quick response along with minimal adverse effects, clinicians should consider treating nasal polyposis with dupilumab in treatment refractory patients.

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Table 1: Baseline demographics, patient characteristics, treatment regimen and outcomes of patients receiving Dupilumab for nasal polyposis (n=29)

Patient characteristics	Male (% , n)	44.8% (n=13)
	Age (mean $\pm$ SD, years)	51.2 $\pm$ 13.8
Comorbidities	Allergic rhinitis (% , n)	89.7% (n=26)
	Asthma (% , n)	82.8% (n=24)
	Atopic dermatitis (% , n)	6.9% (n=2)
	Samter's triad (% , n)	24.1% (n=7)
Nasal polyposis diagnosis and presentation	Anosmia (% , n)	96.6% (n=28)
	Nasal congestion (% , n)	100.0% (n=29)
	Ageusia / hypogeusia (% , n)	72.4% (n=21)
	No polyp noted on CT or rhinoscopy (% , n)	0% (n=0)
	Small polyps in the middle meatus/edema noted on CT or rhinoscopy (% , n)	3.4% (n=1)
	Blocked middle meatus noted on CT or rhinoscopy (% , n)	17.2% (n=5)
	Polyps extending beyond the middle meatus without complete obstruction noted on CT or rhinoscopy (% , n)	41.4% (n=12)
	Massive nasal polyposis noted on CT or rhinoscopy (% , n)	37.9% (n=11)
Previous treatment	Antihistamines/ leukotriene inhibitors (% , n)	72.4% (n=21)

	Nasal irrigation (% , n)	58.6% (n=17)
	Nasal steroids (% , n)	100.0% (n=29)
	Oral steroids (% , n)	44.9% (n=13)
	Immunotherapy (% , n)	24.1% (n=7)
	Polypectomy (% , n)	44.8% (n=13)
	Aspirin desensitization (% , n)	17.2% (n=5)
Dupilumab therapy	Dupilumab dose, median (range), mg	300mg (300 mg) every 2 weeks
	Duration of therapy (mean $\pm$ SD, mo)	10.6 $\pm$ 4.9
	Follow up time (mean $\pm$ SD, mo)	11.1 $\pm$ 4.5
Concurrent therapy ^a	Antihistamines/ leukotriene inhibitors (% , n)	48.3% (n=16)
	Immunotherapy (% , n)	13.8% (n=4)
	Nasal irrigation (% , n)	27.6% (n=8)
	Nasal steroids (% , n)	65.5% (n=22)
	Oral steroids (% , n)	0.0% (n=0)
Outcome	No response ^b (% , n)	6.9% (n=2)
	Partial response ^c (% , n)	10.3% (n=3)
	Complete response ^d (% , n)	82.8% (n=24)
	Persistent anosmia (% , n)	6.9% (n=2)
	Persistent nasal congestion (% , n)	17.2% (n=5)
	Persistent ageusia/ hypogeusia (% , n)	6.9% (n=2)
	Persistent oral steroid use (% , n)	10.3% (n=3)
	Decrease in polyp size noted on CT or	96.6% (n=28)

	rhinoscopy (% , n)	
	No polyps noted on CT or rhinoscopy (% , n)	82.8% (n=24)
	Persistent polyps noted on CT or rhinoscopy (% , n)	17.2% (n=5)
	Small polyps in the middle meatus/edema noted on CT or rhinoscopy (% , n)	10.3% (n=3)
	Blocked middle meatus noted on CT or rhinoscopy (% , n)	3.4% (n=1)
	Polyps extending beyond the middle meatus without complete obstruction noted on CT or rhinoscopy (% , n)	0.0% (n=0)
	Massive nasal polyposis noted on CT or rhinoscopy (% , n)	3.4% (n=1)
Adverse effects	Experienced side effects ^e (% , n)	6.9% (n=2)
Discontinued therapy	Discontinued therapy (% , n)	3.4% (n=1)
	Discontinued due to side effects (% , n)	3.4% (n=1)
	Discontinued due to lack of response (% , n)	0.0% (n=0)

Abbreviations: CT, computed tomography; mo, month; n, number; SD, standard deviation; %, percentage

^a Some medications were prescribed for other co-morbidities

^{b-d} Subjective improvement in nasal congestion, anosmia, and ageusia/ hypogeusia reported by patient. No response indicates patient did not report any changes or worsening in symptoms with dupilumab use. Complete response indicated patient had complete resolution of all symptoms

with dupilumab use. Partial response are all other cases where patients experienced some improvement of symptoms with dupilumab use.

^e side effect included diffuse rash covering >50% body surface area