

Dupilumab as Add-on Therapy for Chronic Rhinosinusitis With Nasal Polyposis in Aspirin Exacerbated Respiratory Disease

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Abstract

Background: Aspirin-exacerbated respiratory disease (AERD) affects 7% of asthmatics. Usual therapies are inadequate for asthma and/or nasal polyposis, leading to decreased quality of life.

Objective: Our objective was to evaluate the efficacy of dupilumab in AERD patients with uncontrolled, chronic rhinosinusitis with nasal polyposis (CRSwNP).

Methods: Patients 18 years and older with a physician diagnosis of AERD and sino-nasal outcome test 22 (SNOT 22) score ≥ 19 despite standard medical therapy were eligible for the study. Patients received one month of placebo dosing, followed by 6 months of dupilumab. Patients were blinded to the order of therapy. Wilcoxon-paired rank sum test was used to compare study outcomes at baseline and the completion of the study.

Results: Ten patients completed the study. The median baseline SNOT 22 score improved from 46 [IQR: 34 to 64.8] to 9.5 [IQR: 2.5 to 19] after 6 months of therapy ($p = 0.0050$). The median baseline Lund MacKay score improved from 21.5 [IQR: 17 to 23.3] to 4 [IQR: 1.2 to 6] after 6 months of therapy ($p = 0.0050$). There was also improvement in the following secondary outcomes: asthma control test (ACT), mini asthma quality of life questionnaire (AQLQ), and University of Pennsylvania Smell Identification test (UPSIT). Exhaled nitric oxide (FeNO), total serum IgE, 24-hour urinary leukotriene E₄, and serum thymus and activation regulated cytokine (TARC) also decreased. There were no significant study-related adverse events.

Conclusion: Dupilumab was highly effective as add-on therapy for CRSwNP in AERD, improving patient-reported outcomes, sinus opacification, and markers of T2 inflammation.

Keywords

aspirin exacerbated respiratory disease, dupilumab, Samter's triad, nasal polyposis, chronic sinusitis with nasal polyposis

Introduction

Aspirin-exacerbated respiratory disease (AERD) is characterized by adult onset asthma, chronic rhinosinusitis with nasal polyposis (CRSwNP), and NSAID intolerance due to nonselective inhibition of cyclooxygenase 1 (COX1), along with dysregulation of cyclooxygenase 2 (COX2). AERD affects 7% of patients with asthma, up to 14% of those with severe asthma¹ and 8-26% of patients with CRSwNP.² Patients with AERD experience symptoms due to asthma and CRSwNP, including nasal congestion, facial pressure, and decreased smell/taste, which significantly affect quality of life.³

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Although the pathophysiology of AERD is incompletely understood, it is characterized by overproduction of Type 2 (T2) pro-inflammatory cysteinyl leukotrienes, along with release of prostaglandin D₂ (PGD₂) from mast cells.⁴ PGD₂ recruits additional T2 effector cells, including eosinophils, basophils, and type 2 innate lymphoid cells.⁵ Additionally, up to 87% of patients with nasal polyposis have nasal colonization with *Staphylococcus aureus*, which further propagates a T2 inflammatory response, releasing IL-4, IL-5, and IL-13.⁶ Thus, therapies targeting the T2 immune pathway have potential to improve symptoms of CRSwNP in AERD.

Therapies for CRSwNP in AERD include leukotriene modifiers and intranasal steroids, both of which often lack efficacy.³ Oral corticosteroids (OCS) remain an effective temporary option, but long term adverse effects limit their use. Patients with AERD also frequently undergo repeat sinus surgery.⁴ Aspirin desensitization is another therapeutic option, but is not performed by all allergists,⁷ and its efficacy may be obviated by adverse effects.⁸ Therefore, management of AERD remains inadequate, and biologic therapy targeting T2 inflammatory pathways may offer additional therapeutic options.

Dupilumab is a fully human VelocImmune[®]-derived monoclonal antibody to the interleukin receptor- α subunit that inhibits both IL-4 and IL-13 signaling pathways,^{9–11} and is approved for atopic dermatitis,¹² moderate to severe persistent asthma,^{13,14} and CRSwNP.¹⁵ A post hoc analysis of patients with AERD included in the CRSwNP dupilumab trial¹⁶ is the only study addressing dupilumab on CRSwNP in patients specifically with AERD. We aimed to prospectively study the efficacy of dupilumab on CRSwNP in AERD.

Methods

This study was conducted at the Rochester Regional Health allergy practice in Rochester, NY from 9/2018 through 9/2019, and was approved by the Rochester Regional Health local institutional review board (IRB). Our target enrollment of 10 patients allowed us to detect a difference in the sino-nasal outcome test 22 (SNOT-22) score of 12.4 with 80% power and a type 1 error rate of 0.05.

Patients 18 years and older with AERD were eligible for the study. AERD was defined by the following: (1) physician diagnosis of asthma, (2) CRSwNP diagnosed by objective evidence of nasal polyposis on nasal endoscopy and/or CT sinus, (3) a convincing clinical history of NSAID sensitivity, consisting of a sino-pulmonary reaction to aspirin/NSAIDs on two separate occasions. An observed aspirin/NSAID reaction was not required for the diagnosis of AERD. Patients were required to have a

SNOT-22 score ≥ 19 despite standard medical therapy. This minimal SNOT-22 was calculated by taking the range of SNOT-22 scores in studies of normal controls (7–10) plus 8.9, which is the minimal clinically meaningful improvement in SNOT-22 score.¹⁷ Continuation of routine medications for AERD, including nasal corticosteroids, inhaled corticosteroids, beta agonists, leukotriene receptor antagonists, 5-lipo-oxygenase inhibitors, chronic aspirin, and oral corticosteroids was permitted. Intranasal corticosteroid injections or placement of corticosteroid-eluting stents during the study period were not permitted. Exclusion criteria for the study included: pregnancy or breast feeding, tobacco use, significant or uncontrolled medical conditions, current treatment with immunosuppressive medications other than corticosteroids, current aeroallergen immunotherapy escalation, or treatment with omalizumab, reslizumab, mepolizumab, or benralizumab within the past four months.

Patients received four weeks of placebo, followed by 6 months of therapy with dupilumab 300 mg/2 ml subcutaneously every 14 ± 3 days. Placebo and dupilumab were both provided by the sponsor, Regeneron Pharmaceuticals (Tarrytown, New York) in an indistinguishable pre-filled syringe. Following the first study visit, doses of placebo or active drug were administered at home or office, per patient-preference.

The following data were collected: demographics (age, race, and gender), time since first NSAID reaction, number of previous sinus surgeries, presence of alcohol-induced sino-pulmonary symptoms, and current and previous medical therapy. A sinus CT was obtained at baseline and completion of the study, and both were reviewed by an independent radiologist for Lund-MacKay scoring.¹⁸ Patients were seen every four weeks, and completed the following at each visit: SNOT-22,¹⁷ asthma control test (ACT),¹⁹ mini asthma quality of life questionnaire (mini AQLQ),²⁰ exhaled nitric oxide (FeNO), and spirometry (per American Thoracic Society guidelines).²¹ The following endpoints were collected at baseline, pre-specified intervals during the study, and at the completion of the study: University of Pennsylvania Smell Identification test (UPSIT),²² complete blood count with differential, total serum IgE, serum tryptase, serum thymus and activation regulated cytokine (TARC), serum PGD₂, and 24-hour urinary leukotriene E₄ (urinary LTE₄). Systemic steroid use was tracked throughout the study. The primary outcome was the change in SNOT-22 from baseline to after six months of therapy. Secondary outcomes included the change from baseline to completion of the study for Lund MacKay scores, UPSIT, ACT, AQLQ, and biomarkers.

Statistical Analysis

Statistical analysis was done using STATA software (StataCorp LLC, College Station, Texas). Baseline characteristics along with both the primary and secondary endpoints for the study patients are reported in medians and interquartile ranges. We used a non-parametric, Wilcoxon-paired rank sum test to compare study outcomes at baseline and the completion of the study. Microsoft Excel software (Office 365, Microsoft Corporation, Redmond, WA 98052) was used to create the figures.

Results

Eleven patients were enrolled for the study, with one dropping out during the study placebo phase. Ten patients completed the study and were included in the data analysis (Table 1). There were 5 males and 5 females. The median age of the cohort was 42.5 years [IQR: 35.3 to 52.8]. The median time since first reaction to NSAIDs was 8 years [IQR: 3.8 to 12.8]. Six of the 10 patients had the diagnosis of AERD confirmed with a physician-supervised aspirin challenge. Seven of the ten patients reported sino-pulmonary symptoms with alcohol consumption. The median number of sinus surgeries was 3.0 [IQR: 2.3 to 3.8], and the median number of OCS courses within the past year was 2.0 [IQR: 2.0 to 3.3]. Two patients were on chronic aspirin therapy, whereas 3 had been on chronic aspirin therapy in the past. Two patients were on chronic OCS (prednisone 10 mg daily). One patient each had been treated with mepolizumab, reslizumab, and one with both mepolizumab and reslizumab.

The median baseline SNOT-22 was 46 [IQR: 34 to 64.8], and this decreased to 9.5 [IQR: 2.5 to 19] after 6 months of therapy ($p=0.0050$) (Figure 1). The median baseline Lund MacKay score was 21.5 [IQR: 17 to 23.3], and this decreased to 4 [IQR: 1.2 to 6] after 6 months of therapy ($p=0.0050$) (Figure 2).

The median baseline ACT score was 19.5 [IQR: 18.3 to 22], and this increased to 25 [IQR: 23.3 to 25] after six months of therapy ($p=0.0168$) (Figure 3(A)). The median baseline mini AQLQ score was 84 [IQR: 68.5 to 93.5], and this increased to 102.5 [IQR: 98.5 to 104.5] after six months of therapy ($p=0.0163$) (Figure 3(B)). The median baseline UPSIT was 11 [IQR: 7.8 to 19.5], and this increased to 32 [IQR: 27.3 to 32.8] after six months of therapy ($p=0.0217$) (Figure 3(C)). There was no difference between the median baseline FEV₁ of 2.83 L [IQR: 2.55 L to 3.14 L] and FEV₁ after six months of therapy of 2.84 L [IQR: 2.35 L to 3.09 L] ($p=0.3863$).

The median baseline FeNO was 25.5 ppb [IQR: 17.5 ppb to 45 ppb], and this decreased to 8.5 ppb [6.5 ppb to 18 ppb] after six months of therapy

Table 1. Demographics of the Study Cohort.

Patient	Age	Sex	Diagnosis Confirmed With ASA Challenge	Time Since 1st NSAID Reaction (Years)	Previous Sinus Surgery	Alcohol-Induced Sino-Pulm Symptoms	OCS Courses Within Last Year	Nasal Corticosteroid	Inhaled Corticosteroid	Long Acting β Agonist	Leukotriene Receptor Antagonist	5 Lipo-Oxygenase Inhibitor	Chronic Aspirin Therapy	Previous Biologic Use
1	37	F	Yes	3	3	Yes	2	Yes	Yes	Yes	No	No	Former	Mepo
2	61	M	No	30	4	No	2	Yes	Yes	Yes	Yes	No	No	No
3	52	F	Yes	3	1	Yes	4	Yes	Yes	Yes	No	Yes	Yes	No
4	53	M	Yes	12	2	Yes	2	Yes	Yes	No	Yes	No	Former	No
5	48	F	No	13	3	No	3	Yes	Yes	Yes	Yes	No	No	Res, Mepo
6	29	M	No	2	3	Yes	6	Yes	Yes	No	Yes	No	No	No
7	36	F	Yes	9	6	Yes	Chronic	Yes	No	No	No	No	Former	No
8	35	F	No	6	1	Yes	Chronic	No	Yes	Yes	Yes	No	No	Res
9	30	M	Yes	7	4	Yes	1	Yes	Yes	Yes	Yes	No	No	No
10	55	M	Yes	15	3	No	2	Yes	Yes	Yes	No	No	Yes	No

Abbreviations: Mepo, mepolizumab; OCS, oral corticosteroid; Res, reslizumab.

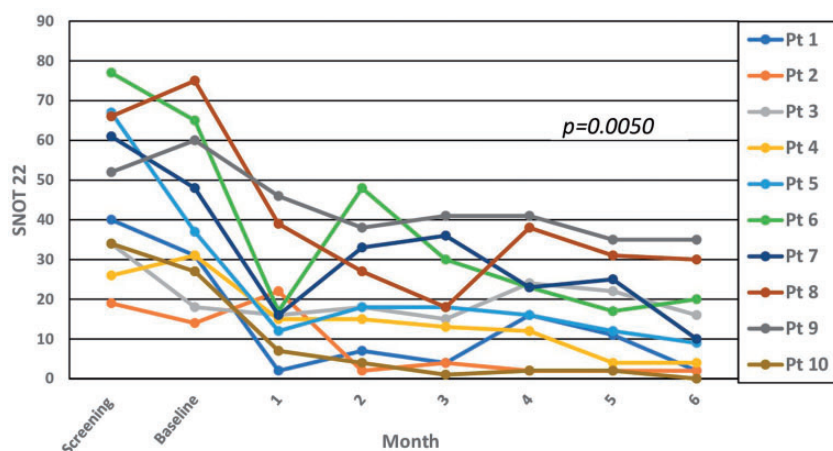


Figure 1. SNOT 22 scores.

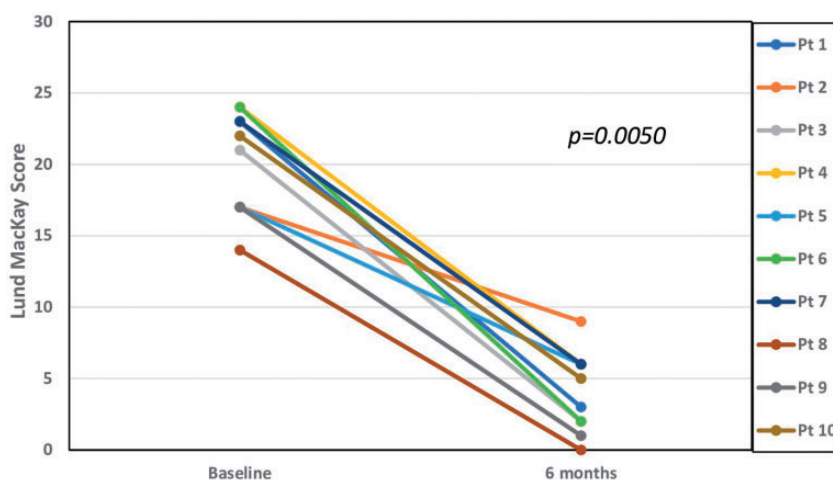


Figure 2. Lund MacKay scores.

($p=0.0107$) (Figure 4(A)). The median baseline total serum IgE was 113 IU/ml [IQR: 35.3 IU/ml to 381.8 IU/ml], and this decreased to 31 IU/ml [IQR: 14.5 IU/ml to 119.5 IU/ml] after six months of therapy ($p=0.0051$) (Figure 4(B)). The median baseline 24-hour LTE_4 was 327 IU/ml [IQR: 223.3 IU/ml to 400 IU/ml], and this decreased to 103 IU/ml [IQR: 67.3 IU/ml to 111.5 IU/ml] after six months of therapy ($p=0.0125$) (Figure 4(C)). The median baseline serum TARC was 0.6 ng/ml [IQR: 0.5 ng/ml to 1.1 ng/ml], and this decreased to 0.3 ng/ml [IQR: 0.2 ng/ml to 0.5 ng/ml] after six months of therapy ($p=0.0050$) (Figure 4(D)). There was no difference between median PGD_2 (67.5 pg/ml [IQR: 56.5 pg/ml to 107.8 pg/ml] to 91 pg/ml [IQR: 48 pg/ml to 98 pg/ml]; $p=0.1386$) or serum tryptase (4 ng/ml [IQR: 3.3 ng/ml to 4.8 ng/ml] to 4.5 ng/ml [3.8 ng/ml to 5/0 ng/ml]; $p=0.0559$) after 6 months of therapy. There was no difference between median baseline absolute eosinophil count (500 cells/mm³ [IQR: 325

cell/mm³ to 650 cells/mm³] to 450 cells/mm³ [IQR: 325 cells/mm³ to 925 cell/mm³]; $p=0.7575$) and after 6 months of therapy.

Prior to study enrollment, 7/10 patients reported sino-pulmonary symptoms with alcohol consumption, with only 1/8 patients who electively consumed alcohol experiencing sino-pulmonary symptoms at study completion ($p=0.0150$). The two patients on chronic OCS both discontinued OCS therapy during the study. The remaining 8 patients received 22 courses of OCS in the 12 months before the study, with 2 patients receiving a total of 3 courses of OCS during the study. Two patients reported local injection site reactions that self-resolved. There were no other study-related adverse events.

Discussion

AERD patients often experience recalcitrant sino-pulmonary symptoms despite maximal therapy.

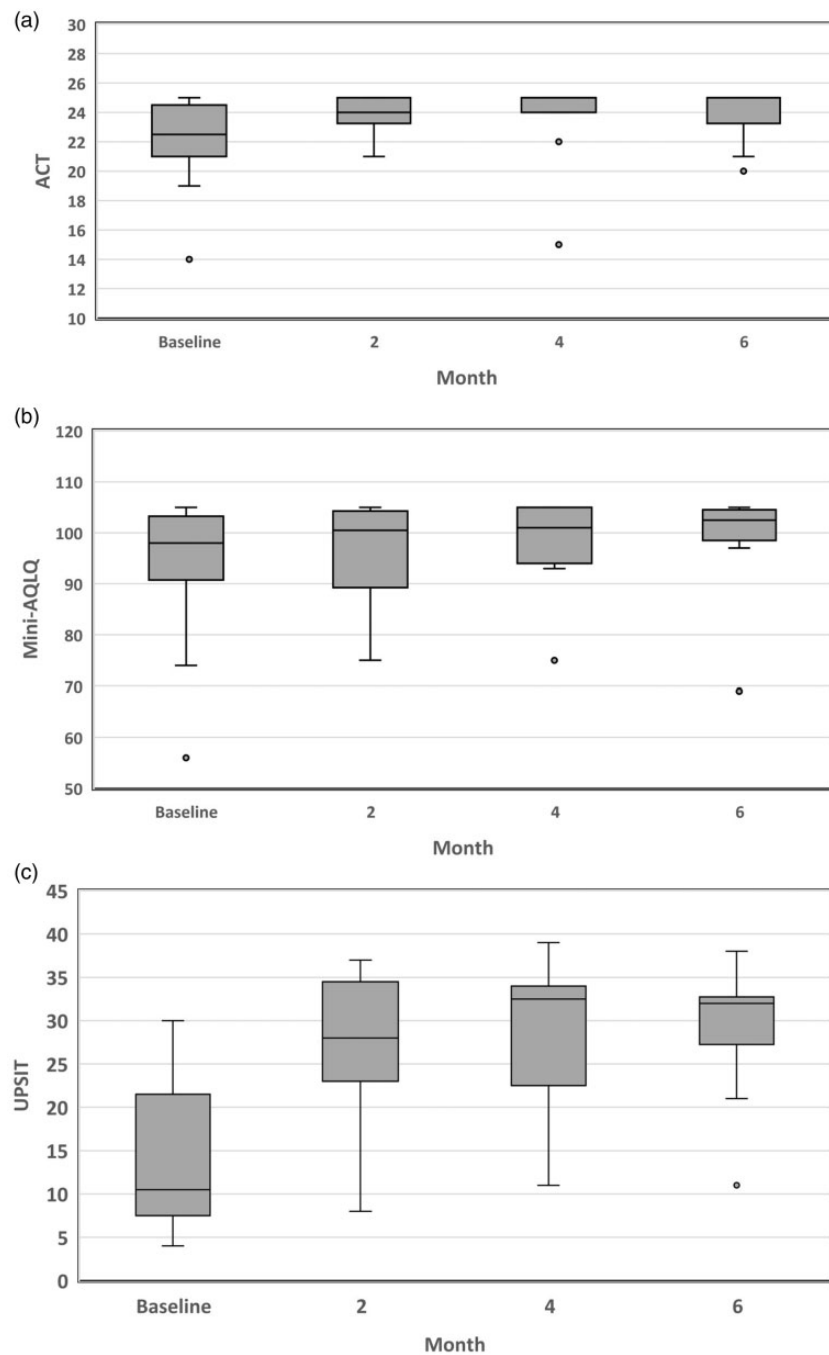


Figure 3. A, Median and range of ACT score. B, Median and range of mini-AQLQ score. C, Median and range of UPSIT.

Patients may develop significant reliance on systemic steroids and frequent surgical intervention.⁴ To our knowledge, this is the first prospective study evaluating the efficacy of dupilumab in uncontrolled CRSwNP in AERD. We demonstrate that dupilumab is efficacious for symptomatic improvement in CRSwNP in AERD based on a significant change in SNOT-22 score. Dupilumab also leads to improvements in sinus

opacification per Lund MacKay scores and T2 inflammatory biomarkers.

Dupilumab has demonstrated efficacy in other T2-high conditions, including asthma and CRSwNP. Dupilumab decreases asthma exacerbations when used as add-on therapy to ICS/LABA in patients with eosinophilic asthma.^{13,14,23} In patients with CRSwNP, dupilumab improves nasal polyp burden, sinus opacification,

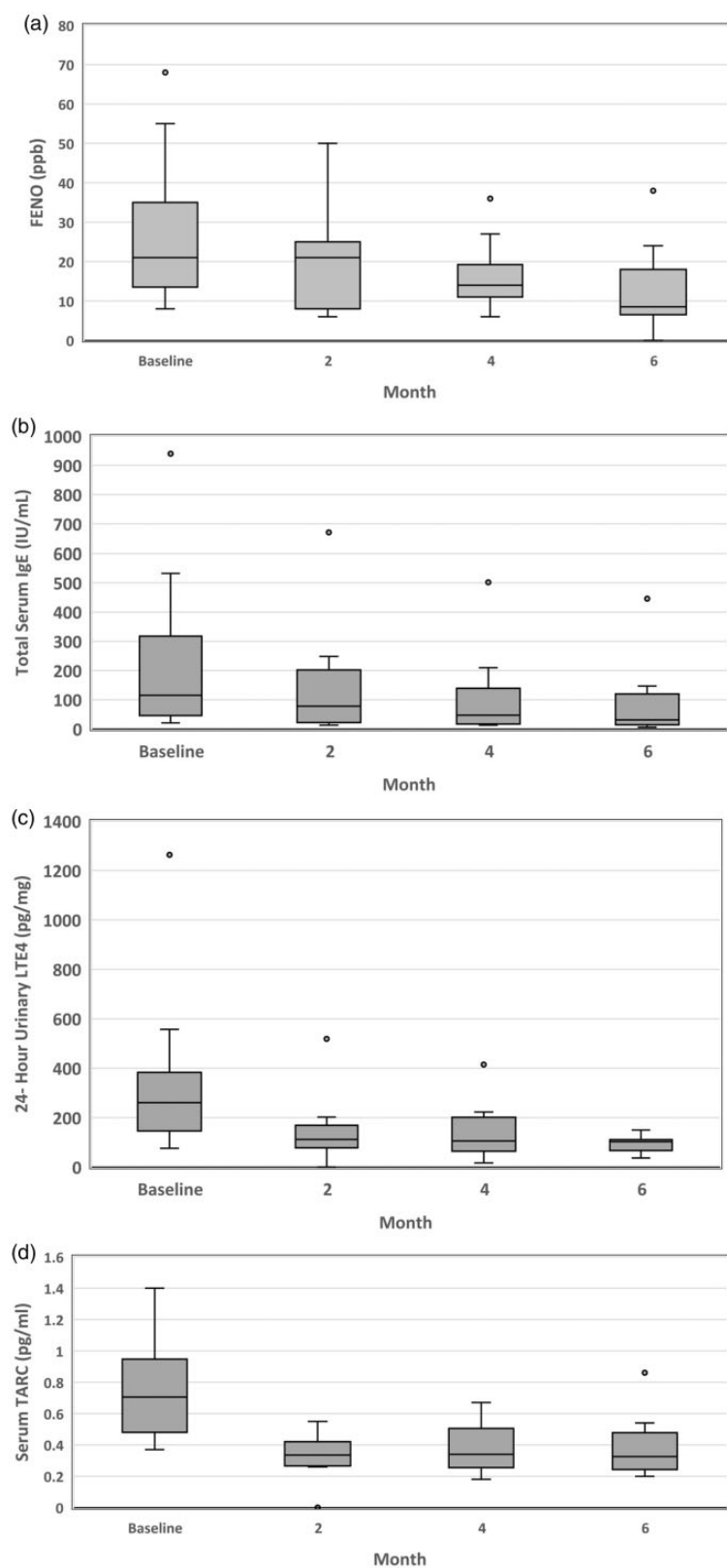


Figure 4. A, Median and range of FeNO. B, Median and range of total serum IgE. C, Median and range of 24-hour urinary LTE₄. D, Median and range of serum TARC.

and severity of symptoms.^{15,24} Despite the T2 inflammation seen in both the upper and lower airways in patients with AERD, there have been no dedicated studies on dupilumab in AERD, though patients with self-reported AERD were included in both the asthma and CRSwNP studies of dupilumab. Preliminary evidence of efficacy of dupilumab in improving symptom scores and sinus opacification in AERD was shown by a retrospective subgroup analysis by Laidlaw et al. of patients with self-reported comorbid AERD from the 2016 study by Bachert et al.^{15,16}

There is also emerging data for other biologics in AERD. Mepolizumab has been shown to be efficacious in AERD in a retrospective subgroup analysis²⁵ and in case reports.^{26,27} Omalizumab has been shown to decrease aspirin-induced bronchospasm in patients with AERD undergoing aspirin desensitization²⁸ and to improve CRSwNP symptoms in case reports.^{29,30} In *post hoc* analyses, reslizumab improves symptoms of self-reported CRSwNP with and without aspirin sensitivity in patients with eosinophilic asthma.³¹

Aspirin desensitization has been a therapeutic option for patients with AERD with inadequately controlled symptoms of CRSwNP and/or asthma.³² Studies have shown that aspirin desensitization slows nasal polyp regrowth, decreases reliance on OCS, and improves nasal congestion, hyposmia, alcohol tolerance, and quality of life.⁴ Aspirin desensitization, however, is time and resource intensive,³² and thus, is performed at relatively few centers. A survey of allergists in 2016 revealed that only 62.5% of respondents perform aspirin desensitization,⁷ and this number may be overly robust due to reporting bias.

Our proof of concept data shows dupilumab significantly improved symptoms of CRSwNP in AERD, as evidenced by a clinically meaningful decrease in median SNOT-22 score and a significant improvement in median Lund Mackay score. Although our study design does not allow for comparison of dupilumab with aspirin desensitization or other biologics, we demonstrate that this is an efficacious option that does not have the logistical considerations of aspirin desensitization.^{25,33} Additionally, dupilumab can be used in the setting of existing polyp burden, and can thus potentially be surgery-sparing, which may also be an advantage compared to other therapies. Our data also suggest that dupilumab decreases the frequency of alcohol-induced sino-pulmonary symptoms in AERD, and decreases the reliance on systemic OCS. Despite our study showing no significant improvement in lung function, dupilumab improved patient-reported asthma symptom scores. We attribute the lack of lung function improvement in our study cohort due to milder asthma with normal lung function at baseline.

Notably, 30% of our cohort had previously tried and failed aspirin therapy, and 20% of patients were on aspirin during the study, implying inadequate control of symptoms despite chronic aspirin therapy. Additionally, 30% of our cohort had tried and failed previous therapy with other biologics aimed at IL5 inhibition. Although we acknowledge our cohort is heterogeneous, our data therefore suggests that dupilumab is a viable option for AERD patients who have previously failed aspirin desensitization and/or anti IL-5 biologics.

There were no significant treatment-related adverse effects or drop-outs due to lack of efficacy in our analysis. Common adverse effects during previous clinical trials of dupilumab included injection site reactions, transient eosinophilia, and URIs. In addition to safety, access to dupilumab also makes it a favorable option for the treatment of AERD, since it can be prescribed by multiple specialists (allergist, pulmonologists, otolaryngologists) and can be self-administered at home.

The unique mechanism of action of dupilumab likely leads to its efficacy in AERD. Dupilumab works through blockade of IL4 and IL13, leading to a significant decrease in FeNO, suggestive of decreased eosinophilic inflammation throughout the sino-pulmonary tract. Additionally, in our study, the improvement in FeNO and other biomarkers of T2 inflammation was seen as early as four weeks after initiation of therapy. Leukotrienes are a key mediator of inflammation in AERD, and our results showed a prompt decrease in urinary LTE₄ levels with dupilumab.

We acknowledge limitations to our analysis. The most important limitation is that this is not a double-blind, placebo controlled study, but rather a prospective case series with a placebo run-in phase. Despite the small cohort in our study, we demonstrated clinically meaningful and statistically significant improvement in not only patient-reported clinical outcomes, but also sinus opacification and objective biomarkers. We hypothesize that a larger study would support these findings, and possibly demonstrate significant improvement in additional outcomes as well. The short duration of our study prevents us from commenting on the durability of the effect of dupilumab in AERD or its surgery-sparing effect, but our follow up was longer than any previously published data.¹⁶ Another weakness of our study was that not all patients had AERD confirmed with aspirin challenge, but this is also reflective of “real world” allergy practice, as was the fact that some patients had previously tried and failed aspirin desensitization and/or therapy with other biologics. Our study was also not designed to formally track the steroid-sparing effect of dupilumab in AERD nor did it directly compare dupilumab with aspirin desensitization. These weaknesses are areas that warrant further study.

In conclusion, our study shows that dupilumab is safe and highly efficacious as add-on therapy in suboptimally controlled CRSwNP in AERD, leading to an improvement in SNOT-22 scores, sinus opacification, along with T2 inflammatory biomarkers.

Disclaimer

This is in regards to the submission for the manuscript entitled *Dupilumab as add-on therapy for chronic rhinosinusitis with nasal polyposis in aspirin-exacerbated respiratory disease*.

This manuscript has been read and approved by all authors. The authors have met all requirements for submission to the journal. The authors personally wrote 100% of the manuscript. This is an original manuscript, not previously published in any format, and not submitted elsewhere.

Authors' Note

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Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Speaker's bureau: Sanofi/Regeneron. Speaker's bureau: Sanofi/Regeneron, Genentech, AstraZeneca, CSL Behring. Dr. Vadmalalai: Nothing to disclose. Dr. Scott: Nothing to disclose.

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