Dupilumab improves patient-reported outcomes in patients with chronic rhinosinusitis with nasal polyps and comorbid asthma

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Clinical Implications

- This analysis of a phase 2a study shows that the addition of dupilumab to mometasone furoate nasal spray improves clinical and patient-reported outcomes in patients with chronic rhinosinusitis with nasal polyps and comorbid asthma.

TO THE EDITOR:

Chronic rhinosinusitis with nasal polyps (CRSwNP) is a common inflammatory condition affecting the upper airways, with chronic symptoms such as nasal congestion, partial (hyposmia) or total (anosmia) loss of smell, anterior/posterior rhinorrhea, and mild facial pain.[1] As many as 66% of patients with CRSwNP have comorbid asthma and suffer from more severe nasal obstruction, higher levels of lower airway inflammation, and worse asthma control than those without CRS.[2,3] Thus, patients with CRSwNP and comorbid asthma have a high disease burden, seriously impacting health-related quality of life (HRQoL).[2,3] Markers of type 2-mediated inflammation and antibody production (eg, IL-5, IgE) are associated with both CRSwNP and asthma pathogenesis.[2]

Dupilumab, a fully human VelocImmune-derived[4,5] monoclonal antibody, blocks the shared receptor component for IL-4 and IL-13, thus inhibiting signaling of both IL-4 and IL-13, key drivers of type 2 diseases such as atopic dermatitis, asthma, and allergic rhinitis.[6] In a 16-week phase 2a study in adults with CRSwNP refractory to intranasal corticosteroids (INCS), adding dupilumab to mometasone furoate nasal spray (MFNS) reduced nasal polyp burden versus MFNS alone and significantly improved nasal congestion and airflow, sense of smell, HRQoL, and other nasal symptoms.[7] We present a subgroup analysis of patients with CRSwNP and comorbid asthma from this study, examining the effect of dupilumab on patient-reported outcomes (PROs) for CRSwNP and asthma, and inflammatory biomarkers.

This randomized, double-blind, placebo-controlled study included a 4-week run-in and 16-week blinded-treatment period.[5] Patients aged ≥18 to 65 years with bilateral NP and chronic symptoms of rhinosinusitis despite INCS treatment ≥2 months, and ≥2 rhinosinusitis symptoms (nasal obstruction, nasal discharge, facial pain/pressure, reduction/loss of smell), were randomized 1:1 to dupilumab 300 mg weekly or placebo, as add-on to MFNS for 16 weeks.

The effect of dupilumab on various NP outcomes in patients with CRSwNP has previously been published.[7] Of 60 patients randomized, 35 (16 dupilumab, 19 placebo) had CRSwNP and comorbid asthma. Baseline demographics and disease characteristics were similar between the study groups (Table E1, available in this article's Online Repository at www.jaci-inpractice.org).

TABLE I. ACQ-5 scores at baseline and change from baseline at week 16 in patients with CRSwNP and comorbid asthma

ACQ-5†	Measure	Mean score (SD) at baseline		LS mean change (SE) from baseline to week 16		LS mean difference for dupilumab vs placebo (95% CI)
		Placebo/MFNS (n = 19)	Dupilumab/MFNS (n = 16)	Placebo/MFNS (n = 12)	Dupilumab/MFNS (n = 15)	
Total overall‡	Total	1.63 (0.87)	1.55 (1.11)	−0.10 (0.20)	−1.19 (0.19)	−1.09 (−1.54, −0.63)***
Item 1§	Woken at night by asthma	1.00 (1.10)	0.88 (1.45)	0.08 (0.24)	−0.91 (0.23)	−0.99 (−1.55, −0.42)**
Item 2§	Awake in morning with asthma symptoms	2.00 (1.37)	1.69 (1.25)	0.01 (0.22)	−1.46 (0.20)	−1.46 (−1.94, −0.99)***
Item 3§	Limited in activities	1.38 (1.20)	1.25 (1.13)	−0.11 (0.23)	−0.93 (0.21)	−0.83 (−1.34, −0.32)**
Item 4§	Shortness of breath	2.19 (1.33)	1.94 (1.24)	−0.29 (0.29)	−1.33 (0.27)	−1.04 (−1.77, −0.31)**
Item 5§	Wheezing time	1.56 (0.63)	2.00 (1.90)	−0.54 (0.36)	−1.50 (0.34)	−0.96 (−1.81, −0.12)*

LS means (and corresponding *P* values) are based on the mixed-effects model with repeated measures.

ACQ-5, 5-Item Asthma Control Questionnaire; *CI*, confidence interval; *CRSwNP*, chronic rhinosinusitis with nasal polyps; *LS*, least squares; *MCID*, minimal clinically important difference; *MFNS*, mometasone furoate nasal spray; *SD*, standard deviation; *SE*, standard error.

*$P < .05$ vs placebo.

**$P < .01$ vs placebo.

***$P < .001$ vs placebo.

†Recall period = 1 wk; score range = 0-6. Lower score indicates better control of asthma.

‡Within-group MCID of 0.5.

§Within-patient MCID of 0.6.

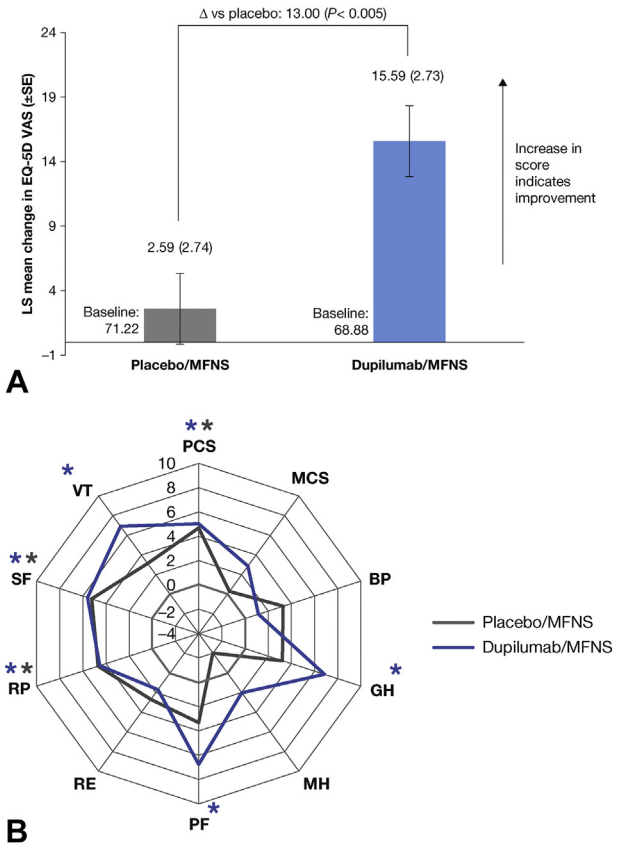

FIGURE 1. Change in generic HRQoL outcomes: least-squares mean change from baseline in EQ-5D self-rated health VAS (mm) score at week 16 (**A**), and in SF-36 individual domain scores at week 16 (**B**). LS means (and corresponding *P* values) are based on the mixed-effects model with repeated measures. Blue asterisks indicate statistically significant improvement from baseline within dupilumab-treated patients ($P < .05$). Gray asterisks indicate statistically significant improvement from baseline within placebo-treated patients ($P < .05$). *BP*, Bodily pain; *EQ-5D*, 5-dimension EuroQoL questionnaire; *GH*, general health; *HRQoL*, health-related quality of life; *MCS*, mental component summary; *MFNS*, mometasone furoate nasal spray; *MH*, mental health; *PCS*, physical component summary; *PF*, physical functioning; *RE*, role-emotional; *RP*, role-physical; *SE*, standard error; *SF*, social functioning; *SF-36*, 36-item Short-Form Health Survey; *VAS*, visual analog scale; *VT*, vitality.

Mean (standard deviation) age was 49.4 (9.0) years; 14 patients were men, and 13 patients (37.1%) had aspirin-exacerbated respiratory disease (42.1% placebo, 31.3% dupilumab). At baseline, patients had moderate-to-severe CRSwNP, and inflammatory biomarker levels were generally similar across treatment groups. Among patients with CRSwNP and comorbid asthma, dupilumab-treated patients (vs placebo) showed a significant improvement in endoscopic NP score ($P < .001$), sense of smell ($P < .001$), Lund-Mackay computed tomography total score ($P < .001$), and significant reduction in CRSwNP disease severity ($P < .001$). Furthermore, a significant improvement in the total 22-item Sino-Nasal Outcome Test score at week 16 was observed in dupilumab-treated patients (vs placebo) ($P < .001$). Dupilumab versus placebo also produced significant improvements in forced expiratory volume in 1 second % predicted ($P = .04$) and 5-item Asthma Control Questionnaire (ACQ-5) total score ($P < .001$) exceeding the minimal clinically important difference (MCID) of 0.5.[7]

In this study, we further assessed the effect of dupilumab on HRQoL in patients with CRSwNP with comorbid asthma using the 5-dimension EuroQoL questionnaire (EQ-5D) visual analog scale (VAS) and 36-item Short-Form Health Survey (SF-36). EQ-5D VAS provides a simple measure of the patient's self-rated health on a vertical virtual analog scale, with scores 0 to 100 mm (worst-best imaginable health state).[8] SF-36 comprises 8 domains assessing physical functioning, social functioning, role limitations due to physical and emotional problems, mental health, energy/vitality, bodily pain, and general health perception. Two summary scores, the physical (PCS) and mental health component summary, are calculated by the aggregation of the 8 SF-36 subscales, to evaluate the physical and mental health, respectively (higher scores indicating better HRQoL).[9] The effects of dupilumab on the individual ACQ-5 scores (woken at night by asthma, awake in morning with asthma symptoms, limited in activities, shortness of breath, wheezing time), as well as inflammatory biomarkers (eosinophils, eosinophil cationic protein, thymus and activation-regulated chemokine, IgE, and periostin), were also assessed.

Changes in clinical outcomes and PROs from baseline to week 16 in patients with CRSwNP and comorbid asthma were reported as least-squares mean values and analyzed using a mixed-effects model with a repeated-measures approach. An unstructured correlation matrix was used to analyze within-patient errors; there was no imputation for missing data. A *P* value <.05 for the comparison between dupilumab and placebo was considered statistically significant.

For each of the individual ACQ-5 scores, a significant difference between treatment groups was observed from baseline to week 16 in favor of dupilumab (Table I). ACQ-5 responder rate (MCID ≥ 0.5) was significantly higher ($P = .038$) in dupilumab-treated patients (62.5%) versus placebo (15.8%). Dupilumab versus placebo produced significant improvements in health status, measured by EQ-5D VAS ($P < .001$; Figure 1, *A*). In dupilumab-treated patients, significant improvements from baseline were observed in 5 SF-36 domains (general health, physical functioning, role-physical, social functioning, and vitality) and PCS ($P < .05$) (Figure 1, *B*). For placebo, change from baseline was statistically significant ($P < .05$) in only 2 domains (role-physical and social functioning) and PCS (Figure 1, *B*). Dupilumab-treated patients (vs placebo) showed a significantly greater reduction from baseline in serum ($P = .002$) and nasal ($P = .04$) secretion levels of total IgE (Table E2, available in this article's Online Repository at www.jaci-inpractice.org).

This subgroup analysis of patients with CRSwNP and comorbid asthma extends the previously reported observations that adding dupilumab to MFNS treatment improves nasal polyp burden, asthma control, lung function, and HRQoL.[7] The effects of dupilumab on CRSwNP-specific clinical outcomes and PROs in patients with asthma were similar in magnitude to those reported for the overall population.[7] Focusing on PROs, the clinical benefit of dupilumab in patients with CRSwNP and comorbid asthma was observed for CRSwNP disease and symptom severity, and asthma control (assessed by ACQ-5 total and individual item scores) reflecting a reduced impact of asthma on daily activities and an improved HRQoL. Significant

improvement from baseline in general health perception, physical functioning, and vitality was only observed with dupilumab treatment and not in the placebo arm.

In conclusion, treatment with dupilumab was associated with an improvement of both clinical and patient-reported NP-specific outcomes, and asthma-specific outcomes in patients with CRSwNP and comorbid asthma.

Acknowledgments

Editorial assistance was provided by Bilge Yoruk, PhD, and Ravi Subramanian, PhD, of Excerpta Medica funded by Sanofi Genzyme and Regeneron Pharmaceuticals.

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The research was sponsored by Sanofi and Regeneron Pharmaceuticals.

Dupilumab is in clinical development for the treatment of chronic rhinosinusitis with nasal polyps and currently has no marketing authorization for this indication.

Conflicts of interest: C. Bachert is the principal investigator of the study, and serves on the advisory boards of ActoBiotics, ALK, ASIT Biotech, AstraZeneca, Novartis, Sanofi, and Stallergenes. P. W. Hellings serves on the advisory board of Regeneron Pharmaceuticals, Inc. J. Mullol is the member of national and international scientific advisory boards (consulting) of and receives fees for lectures and grants for research projects from ALK-Abelló, Allakos, FAES, Genentech, Glenmark, GSK, Mylan, Menarini, MSD, Novartis, Regeneron Pharmaceuticals, Sanofi Genzyme, UCB, and Uriach. R. M. Naclerio serves on the advisory board of ActoBiotics, Genentech, Novartis, and Sanofi; and is on the speaker's bureau of Optinose. J. Chao, N. Amin, J. D. Hamilton, and N. M. H. Graham are employees and shareholders of Regeneron Pharmaceuticals, Inc. A. Grabher, S. Guillonneau, D. Zhang, G. Pirozzi, H. Staudinger, L. P. Mannent, and A. Khan are employees of Sanofi and may hold stock and/or stock options in the company. B. N. Swanson is the former Sanofi employee and may hold stock or stock options in the company. C. Taniou is the employee of Altran Technologies.

Received for publication January 11, 2019; revised March 6, 2019; accepted for publication March 15, 2019.

Available online March 27, 2019.

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2213-2198

https://doi.org/10.1016/j.jaip.2019.03.023

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ONLINE REPOSITORY

TABLE E1. Baseline demographics and disease characteristics of patients with CRSwNP with comorbid asthma

	Placebo/MFNS (n = 19)	Dupilumab/MFNS (n = 16)
Patient characteristic		
Age, mean (SD), y	47.7 (9.9)	51.4 (7.6)
Male, n (%)	7 (36.8)	7 (43.8)
Duration of CRSwNP, mean (SD), y	11.32 (8.93)	8.95 (6.33)
Duration of asthma, mean (SD), y	20.15 (17.40)	15.46 (12.13)
Patients with aspirin-sensitive asthma, n (%)	8 (42.1)	5 (31.3)
Baseline measures of CRSwNP		
Nasal polyps endoscopic score, range 0-8*, mean (SD)	5.53 (1.02)	5.94 (0.85)
CT Lund-Mackay total score, range 0-24*, mean (SD)	19.95 (5.65)	19.07 (4.23)
CRSwNP disease severity VAS (0-10 cm)*, mean (SD)	6.66 (2.36)	6.23 (2.73)
Daily congestion/obstruction score (0-3)†	1.67 (0.74)	1.43 (0.73)
Daily AM loss of smell score† (0-3)†	2.93 (0.24)	2.47 (0.96)
SNOT-22 total score (0-110), mean (SD)*	43.63 (20.66)	40.63 (16.26)
Baseline measures of asthma		
ACQ-5 total score, mean (SD)	1.63 (0.87)	1.55 (1.11)
Baseline FEV_1, mean (SD), % predicted	79.76 (14.55)	82.19 (17.71)
Baseline levels of biomarkers		
Serum blood eosinophil count, mean (SD), 10^9/L	0.55 (0.83)	0.51 (0.25)
Serum ECP, mean (SD), ng/mL	37.26 (48.33)	35.38 (26.27)
Nasal secretion ECP, mean (SD), ng/mL	16.47 (11.49)	41.80 (43.44)
Serum total IgE, mean (SD), IU/mL	233.06 (300.44)	167.13 (153.77)
Nasal secretion total IgE, mean (SD), IU/mL	7.53 (5.64)	20.93 (41.78)
Serum TARC, mean (SD), pg/mL	506.20 (422.59)	506.77 (340.29)
Serum periostin, mean (SD), ng/mL	72.86 (28.52)	80.42 (24.44)
Nasal secretion periostin, mean (SD), ng/mL	6.92 (5.44)	7.27 (5.78)

ACQ-5, 5-item Asthma Control Questionnaire; *AM*, morning; *CRSwNP*, chronic rhinosinusitis with nasal polyps; *CT*, computed tomography; *ECP*, eosinophil cationic protein; *FEV_1*, forced expiratory volume in 1 s; *MFNS*, mometasone fuorate nasal spray; *SD*, standard deviation; *SNOT-22*, 22-item Sino-Nasal Outcome Test; *TARC*, thymus and activation-regulated chemokine; *VAS*, visual analog scale.

*Higher scores indicate worse status.

†Average of the last 7 d before randomization.

TABLE E2. Inflammatory biomarker levels at baseline and change from baseline at week 16 in patients with CRSwNP and comorbid asthma

	Placebo/MFNS group (n = 19)			Dupilumab/MFNS group (n = 16)				
Biomarker	**Baseline mean (SD)**	**Week 16 mean (SD)**	**LS mean change from baseline (SE)**	**Baseline mean (SD)**	**Week 16 mean (SD)**	**LS mean change from baseline (SE)**	**LS mean difference for dupilumab vs placebo at week 16 (95% CI)***	***P* value**
Serum blood eosinophil count, 10^9/L	0.55 (0.83)	0.37 (0.19)	−0.15 (0.17)	0.51 (0.25)	0.53 (0.37)	−0.06 (0.16)	0.09 (−0.34, 0.51)	.682
Serum ECP, ng/mL	37.26 (48.33)	15.57 (11.92)	−14.58 (9.83)	35.38 (26.27)	41.60 (47.60)	6.66 (9.77)	21.25 (−3.70, 46.20)	.094
Nasal secretion ECP, ng/mL	16.47 (11.49)	29.08 (38.72)	26.47 (11.31)	41.80 (43.44)	39.07 (38.19)	16.92 (9.98)	−9.55 (−35.89, 16.80)	.472
Serum total IgE, IU/mL	233.06 (300.44)	128.87 (143.70)	−38.09 (12.22)	167.13 (153.77)	102.07 (119.46)	−86.59 (12.38)	−48.49 (−78.66, −18.33)	.002
Nasal secretion total IgE, IU/mL	7.53 (5.64)	13.77 (21.46)	6.86 (5.03)	20.93 (41.78)	5.53 (4.05)	−5.31 (4.31)	−12.17 (−23.76, −0.57)	.04
Serum TARC, pg/mL	506.20 (422.59)	384.19 (235.65)	−125.80 (44.78)	506.77 (340.29)	288.94 (154.06)	−204.62 (48.99)	−78.82 (−183.10, 25.45)	.135
Serum periostin, ng/mL	72.86 (28.52)	53.05 (18.76)	−17.09 (7.52)	80.42 (24.44)	57.83 (22.27)	−13.83 (6.53)	3.26 (−13.05, 19.57)	.692
Nasal secretion periostin, ng/mL	6.92 (5.44)	8.37 (6.91)	0.64 (2.53)	7.27 (5.78)	4.26 (5.71)	−2.96 (2.16)	−3.60 (−7.60, 0.40)	.076

CI, Confidence interval; *CRSwNP*, chronic rhinosinusitis with nasal polyps; *ECP*, eosinophil cationic protein; *LS*, least squares; *MFNS*, mometasone fuorate nasal spray; *SD*, standard deviation; *SE*, standard error; *TARC*, thymus and activation-regulated chemokine.
*Based on the mixed-effects model with repeated measures.