



# Effect of Dupilumab on Sleep Apnea Severity in Patients With Chronic Rhinosinusitis

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
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
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Patients with chronic rhinosinusitis (CRS) report improved sleep quality after dupilumab, an anti IL4/13 therapy. Concurrent CRS and obstructive sleep apnea (OSA) cases are not rare, and CRS seemingly raises nasal resistance. Thus, we hypothesized that improved sleep quality by dupilumab therapy in CRS patients might be due to lowered nasal resistance and subsequent improvement of unrecognized comorbid OSA. Patients with concurrent CRS and OSA were recruited. Nasal resistance was measured invasively with transnasal pressure and flow data collected during normal respiration in the supine position. Results from the first five participants did not support our hypothesis. Subjective and objective measures for CRS and nasal resistance values were improved with dupilumab therapy in CRS patients with nasal polyps. However, apnea severity and sleep-related subjective parameters did not change. In the patients with CRS without nasal polyps, no significant changes in either CRS or OSA-related measures were observed.

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**Keywords** Dupilumab; Nasal polyps; Airway resistance; Sinusitis; Sleep apnea, obstructive; Therapeutics.

## INTRODUCTION

Sleep quality is commonly impaired in patients with chronic rhinosinusitis (CRS) and patient-reported sleep quality is significantly improved after treatment with dupilumab therapy [1]. Nasal blockage may be the cause for poor sleep quality in CRS patients, but other factors have also been suggested, e.g., influence of inflammatory cytokines on the central nervous system [2]. Nasal resistance may be raised by mucosal congestion or/and nasal polypoidosis in CRS patients, thereby producing a more negative inspiratory swing in pharyngeal intraluminal pressure. This leads to a reduction in pharyngeal cross-sectional area as per the tube law [3]. Accordingly, it can be presumed that high nasal resistance in CRS patients may cause obstructive sleep apnea (OSA) or at least worsen its severity. In fact, overlap of OSA and CRS is not rare and ranges from 10.9% to 64.7% [4-6]. We hypothesized that the patient-reported improvements in sleep quality with dupilumab could have been due, at least partially, to reduction in OSA severity in CRS patients. In this study, the therapeutic effect of dupilumab on OSA severity was investigated, as well as the role of nasal resistance, in patients with concurrent CRS and OSA.

## METHODS

### Participants and Screening

Adults (18 to 80 years) with a previous diagnosis of bilateral CRS with nasal polyps (CRSwNP) or CRS without nasal polyps (CRSsNP) were recruited from the allergy clinics at Brigham and Women's Hospital and the sinus clinics at Massachusetts Eye and Ear Infirmary. To screen the eligible subjects for the study, the allergy specialist (TML) and otorhinolaryngologist (SWK) examined the subjects using anterior rhinoscopy to confirm the diagnosis of CRS. Baseline symptoms associated with CRS were semi-quantified using the 22-item Sinonasal Outcomes Test (SNOT-22) [7]. The participants were tested using home sleep test equipment (Nox T3; Nox Medical, Reykjavik, Iceland), and those with apnea-hypopnea index (AHI) > 10 episodes/hr were enrolled in the study. Exclusion criteria were as follows: body mass index  $\geq 35$  kg/m<sup>2</sup>; concurrent sleep disorder; prior treatment with dupilumab or any other monoclonal antibodies, immunosuppressants, or oral corticosteroids over the preceding 6 weeks; lactating or pregnant females; history of lidocaine allergy; or substance abuse. This study was approved by the Institutional Review Board at Brigham and Women's Hospital (IRB number: 2018P001031), and it was registered on ClinicalTrials.gov (NCT03675022). Written, informed consent was obtained from all subjects before participation in the study.

### Study Protocol

Enrolled patients underwent in-laboratory polysomnography (PSG) for precise diagnosis of OSA severity. Before sleep, anterior and posterior nasal pressures were measured with a pressure sensor attached to a sealed nasal mask and a transnasally inserted 5-French pressure-sensing catheter (Millar Instruments, Houston, TX, USA), respectively. Nasal flow was measured with a pneumotachometer (Hans-Rudolph, Kansas City, MO, USA) attached to the mask. All pressure and flow data were collected during normal respiration for at least 5 minutes in the supine position. The signals were synchronized and saved using Spike 2 software (Cambridge Electronic Design, Cambridge, England). After removing the nasal catheters and the mask, sleep questionnaires, including Epworth Sleepiness Scale (ESS), Pittsburgh Sleep Quality Index (PSQI), and Functional Outcome of Sleep Questionnaire (FOSQ) were obtained. Then, the participants underwent in-laboratory PSG. On the following morning, a computed tomography scan was taken of the sinuses to measure the extent of CRS, which was quantified based on the Lund-Mackay scoring system. Enrolled participants then received a total of eight subcutaneous injections of 300-mg dupilumab (Dupixent; Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA) every two weeks. Approximately two weeks after the last injection, an in-laboratory PSG was repeated, along with other data collected at baseline.

### Data Analyses

Apneas, hypopneas, and arousals were scored using standard American Academy of Sleep Medicine guidelines [8] by a registered sleep technologist blinded to pre-treatment and post-treatment PSG data. Hypopneas were defined as reduction in flow of 30% or more from baseline, lasting at least 10 seconds, and were associated with arousal from sleep or an oxyhemoglobin desaturation of 3% or greater. To obtain nasal resistance values (cm H<sub>2</sub>O/L/sec), transnasal pressure and flow data were picked among three distinct periods containing five or more consecutive stable breaths. Data were analyzed using Matlab software (Mathworks, Natick, MA, USA). The Wilcoxon signed-rank test was used to evaluate pre-treatment and post-treatment changes in measured variables. Changes in the nasal resistance values were compared between CRSwNP and CRSsNP. Since our sample size was too small to assume a Gaussian distribution, a linear mixed model was adopted.

## RESULTS

Following completion of the first six participants, the trial was stopped due to substantial difficulty in finding CRS patients with a high nasal resistance. Nasal resistance values were not measured in the 6th subject; therefore, these analyses were only performed on the first five participants. SNOT-22 showed dupilumab-induced improved trends ( $p = 0.06$ ). The Lund-Mackay score exhibited similar trends. However, AHI, ESS, PSQI, and FOSQ scores were not reduced by dupilumab therapy (Table 1). Of the five subjects in whom nasal resistance was measured, the two with CRSwNP exhibited dupilumab-induced reduced nasal resistance (median reduction of 1.83 cm H<sub>2</sub>O/L/sec and 8.55 cm H<sub>2</sub>O/L/sec, respectively, at transnasal pressure of 1.5 cm H<sub>2</sub>O). However, only one of the three patients with CRSsNP showed a reduction in nasal resistance (Table 2). Nasal resistance values showed marginally significant reduction ( $p = 0.06$ ) in CRSwNP patients, but not in CRSsNP patients. Despite these declines in nasal resistance in the two CRSwNP patients, AHI did not change significantly in either CRSwNP or CRSsNP patients.

## DISCUSSION

Some previous studies showed significant reduction in AHI after resolution of nasal blockage. For example, the mean AHI significantly declined from 33.5/h to 29.4/h after endoscopic sinus surgery in patients with OSA and CRS [9]. In another study where nasal resistance was measured in CRSwNP patients, nasal resistance values and PSQI scores were significantly reduced after endoscopic sinus surgery. The mean AHI also significantly declined accordingly from 13.3/h to 11.2/h [10]. However, in the other study, there was no significant association between the se-

**Table 1.** Demographics and measured parameters of the study participants

Subject no.	Age (yr)	Sex	BMI (kg/m <sup>2</sup> )	NP	SNOT-22		LM score		AHI		ESS		PSQI		FOSQ	
					Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	47	M	24.9	No	65	50	12	3	28.0	19.9	1	4	8	5	17.9	18.0
2	57	F	32.0	No	71	27	2	2	27.6	29.4	15	12	9	4	14.8	13.0
3	51	F	31.0	Yes	81	37	23	13	41.9	42.6	15	15	9	10	11.8	15.5
4	53	F	28.9	No	35	44	0	0	37.5	51.5	11	11	5	7	16.7	17.4
5	51	M	27.5	Yes	38	14	17	12	18.0	53.0	10	10	12	8	15.9	17.8
6	48	M	33.0	Yes	37	3	24	8	39.4	39.6	5	5	3	2	18.8	19.3
p-value					0.06		0.10		0.22		> 0.99		0.25		0.22	

BMI, body mass index; NP, nasal polyps; SNOT-22, 22-item sinonasal outcomes test; LM, Lund-Mackay; AHI, apnea-hypopnea index; ESS, Epworth Sleepiness Scale; PSQI, Pittsburgh Sleep Quality Index; FOSQ, Functional Outcome of Sleep Questionnaire.

**Table 2.** Pre-treatment and post-treatment nasal resistance values at transnasal pressure of 1.5 cm H<sub>2</sub>O

Subject no.	NP	R <sub>n_pre</sub> (cm H <sub>2</sub> O/L/sec)	R <sub>n_post</sub> (cm H <sub>2</sub> O/L/sec)
1	No	1.66 (1.63–1.68)	2.94 (2.50–3.16)
2	No	4.17 (4.02–4.48)	1.61 (1.22–1.98)
3	Yes	5.03 (3.89–6.23)	3.20 (3.20–3.33)
4	No	2.88 (2.69–2.95)	3.12 (2.21–3.83)
5	Yes	15.17 (11.13–15.20)	6.62 (6.06–8.15)

Values are presented as the median (interquartile range) of three resistance values picked from distinct periods containing five or greater consecutive stable breaths signals.

NP, nasal polyps; R<sub>n\_pre</sub>, pre-treatment nasal resistance; R<sub>n\_post</sub>, post-treatment nasal resistance.

verity of OSA and the severity of CRS or between the severity of OSA and the presence of NP [4]. Furthermore, a retrospective cohort study on CRS patients revealed that CRSsNP patients had significantly higher odds of OSA than CRSwNP patients [5]. Similar results were observed in this study. Based on our small sample, we could not adequately test our hypothesis. Nevertheless, for the six subjects we studied, we did not find significant reduction in AHI after dupilumab therapy, even for the two patients with CRSwNP in whom dupilumab decreased nasal resistance (Tables 1 and 2). Taken together, high nasal resistance in CRS patients appears to have little, if any, impact on the development or worsening of OSA. High upper airway resistance at the soft palate level, not high nasal resistance, might significantly influence the OSA severity. A future study that measures the upper airway resistance at multiple sites before and after treatment of CRS might be required to prove it. Regarding the small number of participants, we originally planned to enroll 22 subjects. Under the assumption that a 50% reduction in AHI is a clinically meaningful change in OSA severity and the standard deviation of the change in AHI is 40%, 20 individuals were calculated to have 98% power to detect this difference with  $\alpha = 0.05$ . Enrolling 22 subjects was initially scheduled, given the likelihood of dropouts. However, the trial was prematurely terminat-

ed due to the difficulties in finding eligible subjects, which is a limitation of the present study. Another limitation is the absence of data on various nose-related and OSA-related factors such as nasal septal deviation, hypertrophy of the inferior turbinate, palatine tonsil size, and palate-tongue position grades. This absence could have influenced the negative association between nasal resistance and AHI changes.

To summarize this study, OSA severity did not change while the nasal resistance declined in CRSwNP patients. Neither nasal resistance nor OSA severity significantly changed in CRSsNP patients. A future study will be needed to elucidate the mechanism of improved sleep quality after dupilumab therapy in CRS patients.

#### Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

#### Author Contributions

Conceptualization: Charles A. Czeisler, Tanya M. Laidlaw, Andrew Wellman. Data curation: Sang-Wook Kim. Formal analysis: Sang-Wook Kim. Funding acquisition: Charles A. Czeisler, Tanya M. Laidlaw, Andrew Wellman. Investigation: Sang-Wook Kim, Scott A. Sands, Daniel Vena. Methodology: Sang-Wook Kim, Scott A. Sands, Daniel Vena, Lauren B. Hess, Nicole A. Calianese, Robert James Konefal. Project administration: Lauren B. Hess, Nicole A. Calianese, Robert James Konefal. Resources: Lauren B. Hess, Nicole A. Calianese. Software: Sang-Wook Kim, Scott A. Sands, Daniel Vena. Supervision: Charles A. Czeisler, Tanya M. Laidlaw, Andrew Wellman. Validation: Luigi Taranto-Montemurro, Ali Azarbarzin. Visualization: Sang-Wook Kim, Scott A. Sands. Writing—original draft: Sang-Wook Kim, Tanya M. Laidlaw, Andrew Wellman. Writing—review & editing: Luigi Taranto-Montemurro, Ali Azarbarzin, Lauren B. Hess, Nicole A. Calianese, Robert James Konefal, Scott A. Sands, Daniel Vena, Charles A. Czeisler.

#### Conflicts of Interest

The disclosures of conflict of interest of all authors are provided in Appendix 1.

#### Funding Statement

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## APPENDIX 1. DISCLOSURES OF CONFLICT OF INTEREST

SWK was supported by the Gyeongsang National University Fund for Professors on Sabbatical Leave, 2018. AW works as a consultant for Somnifix, Nox, Apnimed, and Inspire, and has received grants from Somnifix and Regeneron Pharmaceuticals, Inc. LTM works as chief scientific officer at Apnimed. AW and LTM have a financial interest in Apnimed. AA serves as consultant for Somnifix and Apnimed. SAS serves as consultant for Cambridge Sound Management. TML has served on scientific advisory boards for GlaxoSmithKline, Sanofi-Genzyme, Regeneron Pharmaceuticals, Inc., and AstraZeneca, and has received research grants from GlaxoSmithKline and Regeneron Pharmaceuticals, Inc. Dr. Czeisler reports grants to BWH from FAA, NHLBI, NIA, NIOSH, NASA, and DOD; is/was a paid consultant to AARP, American Academy of Dental Sleep Medicine, Eisenhower Medical Center, Emory University, Inselspital Bern, Institute of Digital Media and Child Development, Klarman Family Foundation, M. Davis and Co, Physician's Seal, Sleep Research Society Foundation, State of Washington Board of Pilotage Commissioners, Tencent Holdings Ltd, Teva Pharma Australia, UC San Diego, University of Washington, and Vanda Pharmaceuticals Inc, in which Dr. Czeisler also holds an equity interest; received travel support from Annenberg Center for Health Sciences at Eisenhower, Aspen Brain Institute, Bloomage International Investment Group, Inc., UK Biotechnology and Biological Sciences Research Council, Bouley Botanical, Dr. Stanley Ho Medical Development Foundation, European Biological Rhythms Society, German National Academy of Sciences (Leopoldina), Illuminating Engineering Society, National Safety Council, National Sleep Foundation, Society for Research on Biological Rhythms, Sleep Research Society Foundation, Stanford Medical School Alumni Association, Tencent Holdings Ltd, University of Zurich, and Vanda Pharmaceuticals Inc, Ludwig-Maximilians-Universität München, National Highway Transportation Safety Administration, Office of Naval Research, Salk Institute for Biological Studies/Fondation Ipsen; receives research/education support through BWH from Cephalon, Mary Ann & Stanley Snider via Combined Jewish Philanthropies, Harmony Biosciences LLC, Jazz Pharmaceuticals PLC Inc, Johnson & Johnson, NeuroCare, Inc., Philips Respironics Inc/Philips Homecare Solutions, Regeneron Pharmaceuticals, Regional Home Care, Teva Pharmaceuticals Industries Ltd, Sanofi SA, Optum, ResMed, San Francisco Bar Pilots, Sanofi, Schneider, Simmons, Sysco, Philips, Vanda Pharmaceuticals; is/was an expert witness in legal cases, including those involving Advanced Power Technologies, Aegis Chemical Solutions LLC, Amtrak; Casper Sleep Inc, C&J Energy Services, Catapult Energy Services Group, LLC, Covenant Testing Technologies, LLC, Dallas Police Association, Enterprise Rent-A-Car, Espinal Trucking/Eagle Transport Group LLC/Steel Warehouse Inc, FedEx, Greyhound Lines Inc/Motor Coach Industries/FirstGroup America, Pomerado Hospital/Palomar Health District, PAR Electrical Contractors Inc, Product & Logistics Services LLC/Schlumberger Technology Corp/Gelco Fleet Trust, Puckett Emergency Medical Services LLC, South Carolina Central Railroad Company LLC, Union Pacific Railroad, United Parcel Service/UPS Ground Freight Inc, and Vanda Pharmaceuticals; serves as the incumbent of an endowed professorship provided to Harvard University by Cephalon, Inc.; and receives royalties from McGraw Hill, and Philips Respironics for the Actiwatch-2 and Actiwatch Spectrum devices. Their interests were reviewed and are managed by Brigham and Women's Hospital and Mass General Brigham in accordance with their conflict of interest policies.