Real-world dupilumab treatment reduced healthcare resource utilization and medication use in patients with CRSwNP

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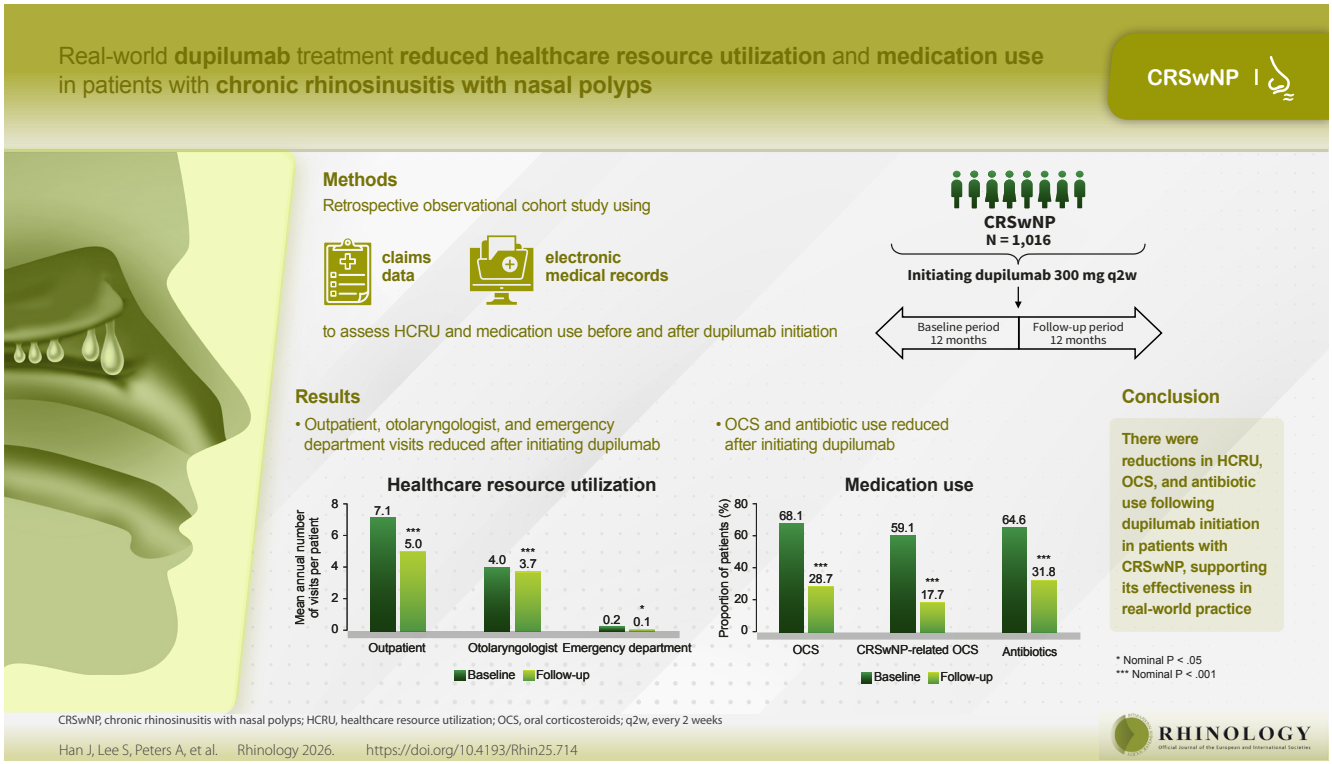

Abstract

Background: Evidence of dupilumab's real-world effectiveness in patients with chronic rhinosinusitis with nasal polyps (CRSwNP) in US clinical practice is limited.

Objective: To investigate healthcare resource utilization (HCRU) and medication use in patients with CRSwNP before and after dupilumab initiation in real-world US clinical practice.

Methods: This retrospective observational study included adults with CRSwNP who initiated dupilumab 300 mg every 2 weeks between June 2019 and June 2022. Data including claims and electronic health records were extracted from the OM1 Real-World Data Cloud and Reg-ENT Registry. Medication use, healthcare visits, sinus procedures, and imaging were assessed during the 12 months before (baseline) and after (follow-up) dupilumab initiation.

Results: The study comprised 1,016 patients (mean age 53.8 years, 46.1% female). Annual mean [standard deviation] number of visits per patient was lower during follow-up vs baseline for outpatient (5.0 [5.2] vs 7.1 [6.0]), otolaryngologist (3.7 [6.7] vs 4.0 [6.1]) and emergency department visits (0.1 [0.6] vs 0.2 [0.6]). The proportion of patients prescribed oral corticosteroids for any reason was lower during follow-up (28.7% vs 68.1%, respectively. Fewer patients were prescribed antibiotics (31.8% vs 64.6%) and CRSwNP related oral corticosteroids (17.7% vs 59.1%), and fewer patients underwent nasal endoscopy (47.5% vs 71.2%) and CT scan (4.5% vs 22.1%) during follow-up than at baseline.

Conclusions: These findings suggest an association between dupilumab treatment and reductions in HCRU and medication use in patients with CRSwNP, and provide supportive evidence of dupilumab's real-world effectiveness.

Key words: biologic treatment, chronic rhinosinusitis, nasal polyps, sinusitis

Plain Language Summary

Chronic rhinosinusitis with nasal polyps (CRSwNP) is a condition in which growths called nasal polyps block the nasal passages. Symptoms of CRSwNP include nasal congestion, runny nose, and loss of smell. CRSwNP can reduce quality of life and lead to high healthcare costs. While initial therapies such as saline irrigation and intranasal corticosteroids can help manage symptoms, they are not effective in all patients. In such cases, oral corticosteroids may be recommended; however, their use is limited to short courses due to potential side effects. While surgery to remove nasal polyps can improve symptoms for a longer period, polyps will often grow back. Dupilumab has been shown to alleviate symptoms and reduce polyp size in clinical trials; however, further evidence is needed from real-world practice. This article presents the findings of a study that investigated the impact of dupilumab treatment on patients with CRSwNP in US medical practice. The study evaluated the need for healthcare services and medication before and after starting dupilumab treatment, based on data from insurance claims and electronic health records. It was found that patients with CRSwNP needed fewer healthcare visits, underwent fewer nasal procedures, and used fewer medications in the year after starting dupilumab. These findings provide supportive evidence of dupilumab's effectiveness in treating CRSwNP in real-world US medical practice.

Introduction

Chronic rhinosinusitis with nasal polyps (CRSwNP) is characterized by persistent inflammation of the nasal cavity and paranasal sinuses, and is predominantly associated with a type 2 inflammatory signature [1-3]. Symptoms include nasal congestion/obstruction, rhinorrhea, facial pain or pressure, and a diminished or loss of sense of smell [1]. Patients often have coexisting type 2 inflammatory conditions such as asthma and/or aspirin exacerbated respiratory disease (AERD), which commonly share type 2 pathophysiology [4]. CRSwNP is associated with poor health-related quality of life and a high cost burden, with annual overall healthcare costs in the United States of America (USA) estimated to be $5.7 billion in 2019 [5]. Patients with CRSwNP and coexisting asthma or AERD have increased disease severity and are considered a difficult-to-treat population. These patients require higher doses of corticosteroids and have higher recurrence of nasal polyps (NP) and rates of revision surgery [6-10].

First-line treatments for managing CRSwNP include intranasal saline and topical corticosteroids. In cases where these treatments are insufficient for controlling symptoms, oral corticosteroids (OCS) may offer short-term symptom relief [11]. Functional endoscopic sinus surgery may provide longer-lasting disease control in patients who do not have sufficient response to first-line treatments alone [12]. However, due to the chronic and recurrent nature of CRSwNP, surgical interventions may result in only temporary symptom improvement, because NP often recur after surgery [13].

Biologics targeting type 2 inflammation present a potential option for patients with severe CRSwNP, offering an alternative to repeated courses of corticosteroids and/or surgery. Dupilumab, a fully human monoclonal antibody approved for the treatment of CRSwNP, blocks the shared receptor component for interleukin-4 and interleukin-13, which are central drivers of type 2 inflammation [14,15]. In randomized, placebo-controlled studies, dupilumab treatment improved objective and patient-reported CRSwNP outcomes in patients with severe CRSwNP and showed safety consistent with the known dupilumab safety profile [16]. Randomized controlled clinical trials evaluate the efficacy of a treatment in a controlled setting and on a selected population, which may not reflect real-world practice [17]. While evidence on the real-world effectiveness of dupilumab in patients with CRSwNP is emerging in the European Union (EU) and Canada [18-22], it remains limited in the US. This study aims to assess the effectiveness of dupilumab in terms of healthcare resource utilization (HCRU), medications, and tolerability in patients with CRSwNP in real-world settings in the US.

Materials and methods

Study design and patients

This was a retrospective observational study of a cohort of patients with CRSwNP who initiated dupilumab 300 mg every 2 weeks between June 2019 and June 2022. Data were extracted from the OM1 Real-World Data Cloud (OM1, Inc., Boston, MA, USA), including data in the Reg-ENT Registry. The OM1 Real-World Data Cloud is a continuously updated, deterministically linked, multisource dataset derived from electronic medical records (EMR), claims, and other data. The medical and pharmacy claims contain billing and coding history from patients who visited acute care facilities, ambulatory medical and surgery centers, and specialty clinics. The Reg-ENT Registry provides data collected from otolaryngologists' EMR systems, updated quarterly, depending on the practice. The data collected include encounters, procedures, laboratory results, e prescribing data, and clinical observations.

Patients included in this analysis were at least 18 years old when they initiated dupilumab and had at least one diagnosis code for chronic rhinosinusitis (CRS) and at least one diagnosis code for NP within 12 months before or on the dupilumab initiation date. In addition, patients had linked EMR and claims data for at least 12 months before and after the dupilumab initiation date.

The exclusion criteria were as follows: patients who had undergone an endoscopic sinonasal surgery within 12 months before or after the index date; those who were prescribed, dispensed, or administered mepolizumab, benralizumab, omalizumab, reslizumab, or dupilumab within the 12 months before the index date; and patients diagnosed with cancer of the nasal cavity or sinus at any time before, or at the index date. Additionally,

patients with atopic dermatitis were excluded.
The index date was defined as the date of dupilumab initiation (i.e. prescription or fill date). The baseline period covered the 12 months before and including the index date. The follow-up period was the 12 months after, but not inclusive of, initiation of dupilumab.

Objectives

The primary objective of this study was to describe and compare real-world HCRU and medication use in patients with CRSwNP before and after the initiation of dupilumab treatment. The secondary objective was to characterize patient demographics, comorbidities, healthcare visits, CRS-related surgical and imaging procedures, and medications. Adverse events of special interest (AESIs) were assessed as exploratory outcomes.

Assessments

Baseline assessments of patients included demographics, comorbidities as defined by the Charlson Comorbidity Index (23), type 2 inflammation-driven comorbidities (including asthma, AERD, allergic rhinitis, allergic conjunctivitis, atopic dermatitis, eosinophilic esophagitis), healthcare visits, CRS-related surgical and imaging procedures, medications, and insurance type.
HCRU was assessed in baseline and follow-up periods and included healthcare visits (outpatient, otolaryngologist visit, emergency department visit, inpatient, ambulatory [day surgery and urgent care], and number of hospital days), sinus procedures, and sinus-related imaging (computed tomography [CT]; magnetic resonance imaging [MRI]).
The following medications were assessed in both baseline and follow-up periods: OCS, prescription intranasal corticosteroids (INCS), and antibiotics. Prescription and fill records were used as proxies for actual medication use.
CRSwNP-related measures were defined as within 5 days of a CRS and/or NP diagnosis. CRSwNP-related OCS measures included the number of prescriptions/fills, OCS dose (reported as mg per patient in prednisone equivalents), chronic OCS use (defined as a cumulative supply of >30 days), and short courses (defined as steroid use with a duration of ≤14 days, with a gap of at least 7 days between courses).
AESIs were defined as gastrointestinal ulcer or bleed, epistaxis/nosebleed, conjunctivitis, eosinophilia, pericarditis, anaphylaxis, herpes simplex virus infection, opportunistic infection, serious infection (any of aseptic meningitis, bacterial meningitis, encephalitis, cellulitis, endocarditis, pneumonia [excluding tuberculosis], pyelonephritis, septic arthritis, osteomyelitis, bacteremia and sepsis, candidal sepsis, candidiasis of the vulva or vagina, invasive candidiasis, chronic disseminated candidiasis, acute disseminated candidiasis, cryptococcus, or aspergillosis), or parasitic infection.

Table 1. Patient demographics.

	N = 1,016
Mean (SD) age, years	53.8 (14.1)
Age category, years	
18–39	165 (16.2)
40–64	606 (59.6)
≥65	245 (24.1)
Female	468 (46.1)
Race*	
Caucasian	667 (78.9)
Black or African American	117 (13.8)
Asian	28 (3.3)
Other	33 (3.9)
Ethnicity*	
Not Hispanic or Latino	652 (89.9)
Hispanic or Latino	73 (10.1)
Insurance type	
Commercial	414 (40.7)
Medicare	164 (16.1)
Medicaid	15 (1.5)

All data are n (%), unless otherwise stated. SD, standard deviation.
*Excludes those classed as "unknown" (n = 171 for race and n = 291 for ethnicity).

Statistical analyses

Healthcare visits, sinus procedures, sinus-related imaging, and medications in the overall cohort were statistically tested and compared between the baseline and follow-up periods. Categorical outcomes were assessed using the Chi-squared test, and healthcare visits were assessed using the Wilcoxon test.
AESIs were assessed by incidence during both the baseline and follow-up periods. Data were summarized descriptively. The AESI analysis included patients regardless of the duration of their available linked data following initiation of dupilumab.
A segmented regression approach was used to analyze an interrupted time series of monthly HCRU during the baseline and follow-up periods for the following healthcare visits: outpatient (defined as all general practitioner and specialist visits), otolaryngologist, emergency department, inpatient, and ambulatory. The time series of outcomes data was divided into two segments: monthly rates during the baseline period and monthly rates during the follow-up period. The regression model calculated changes in intercept (level) and slope (trend) in the baseline and follow-up periods. A positive slope indicates an increase in HCRU, while a negative slope indicates a decrease.

Table 2. Healthcare visits during the baseline and follow-up periods.

	Entire cohort *			Patients with visits †	
	Baseline period (N = 1,016)	Follow-up period (N = 1,016)	Nominal P value	Baseline period (N = 1,016)	Follow-up period (N = 1,016)
Outpatient, n (%)	—	—		1,011 (99.5)	943 (92.8)
Number of visits, mean (SD)	7.1 (6.0)	5.0 (5.2)	< .001	7.1 (6.0)	5.4 (5.2)
Otolaryngologist	—	—		681 (67.0)	608 (59.8)
Number of visits, mean (SD)	4.0 (6.1)	3.7 (6.7)	< .001	6.0 (6.6)	6.2 (7.7)
Emergency department	—	—		121 (11.9)	90 (8.9)
Number of visits, mean (SD)	0.2 (0.6)	0.1 (0.6)	.024	1.6 (0.9)	1.7 (1.2)
Ambulatory	—	—		663 (65.3)	509 (50.1)
Number of visits, mean (SD)	1.9 (2.4)	1.2 (2.0)	< .001	2.9 (2.4)	2.4 (2.3)
Inpatient	—	—		46 (4.5)	32 (3.1)
Number of visits, mean (SD)	0.1 (0.3)	<0.1 (0.3)	.111	1.2 (0.7)	1.4 (0.8)
Number of hospital days, mean (SD)	1.0 (16.2)	0.5 (6.5)	.110	22.6 (73.5)	14.3 (34.5)

Nominal P value calculated using Wilcoxon test. Q, quartile; SD, standard deviation. * Calculated among the entire cohort (N = 1,016). † Calculated among patients with at least one of the given visit type.

Results

Demographics and patient characteristics at baseline

The overall cohort comprised 1,016 patients, and demographics are shown in Table 1. The mean (standard deviation [SD]) age was 53.8 (14.1) years and 46.1% of patients were female. Most were Caucasian (78.9%) and non-Hispanic or Latino (89.9%). A total of 40.7% of patients had commercial insurance.

The most prevalent coexisting type 2 inflammatory diseases were allergic rhinitis (71.3%) and asthma (57.0%). The mean (SD) Charlson Comorbidity Index was 0.9 (1.1), with 86.6% of patients included in the 0–1 category (Table S1). Other comorbidities commonly observed were diabetes (9.4%) and chronic obstructive pulmonary disease (8.3%). A small proportion of patients (2.0%) had a record of AERD.

During the baseline period, patients had a mean (SD) of 7.1 (6.0) outpatient visits (Table 2). Of the patients with at least one of the given visit types, approximately two-thirds consulted an otolaryngologist (67.0%), with a mean (SD) of 6.0 (6.6) visits per patient. Additionally, around two-thirds of patients had an ambulatory visit (65.3%), with a mean (SD) of 2.9 (2.4) visits per patient. Most patients had a nasal endoscopy (71.2%). Approximately one-quarter of patients had sinus-related CT scans (22.1%), with no reported sinus-related MRIs (Table 3).

Most patients used OCS during the baseline period (68.1%), and more than half used antibiotics (64.6%) (Table 3).

HCRU during the follow-up period

HCRU during the follow-up period is shown in Table 2. The proportion of patients who had a sinus-related procedure was lower during the follow-up period than the baseline period for nasal endoscopy (47.5% vs 71.2%, respectively; nominal P < .001). Fewer patients had a sinus related CT scan during the follow-up period than the baseline period (4.5% vs 22.1%; nominal P < .001).

The mean (SD) number of healthcare visits per patient was lower during the follow up period compared with baseline for outpatient (5.0 [5.2] vs 7.1 [6.0]; nominal P < .001), ambulatory (1.2 [2.0] vs 1.9 [2.4]; nominal P < .001), otolaryngologist (3.7 [6.7] vs 4.0 [6.1]; nominal P < .001), and emergency department visits (0.1 [0.6] vs 0.2 [0.6]; nominal P < .05).

The mean (SD) number of inpatient visits was 0.1 (0.3) during baseline and <0.1 (0.3) during follow-up (nominal P = .111). Focusing only on patients with visits of the given types, the mean (SD) number of outpatient visits per patient decreased from 7.1 (6.0) during the baseline period to 5.4 (5.2) during the follow-up period. Similarly, ambulatory visits and the number of hospital days were lower during the follow-up period compared with the baseline period (2.9 [2.4] vs 2.4 [2.3] and 22.6 [73.5] vs 14.3 [34.5], respectively).

Association between dupilumab initiation and HCRU

For outpatient visits, the regression analysis slope (standard error [SE]) during baseline was 43.9 (9.9) (nominal P < .001), indicating an increase in monthly outpatient visits through the 12 months before dupilumab initiation (Figure 1A and Table S2). The number of outpatient visits decreased from the last observation before dupilumab initiation to the first observation after dupilumab initiation (level change [SE] -210.9 [97.3]; nominal P < .05). This downward trend was maintained through the follow-up period (slope [SE] -74.9 [14.0]; nominal P < .0001).

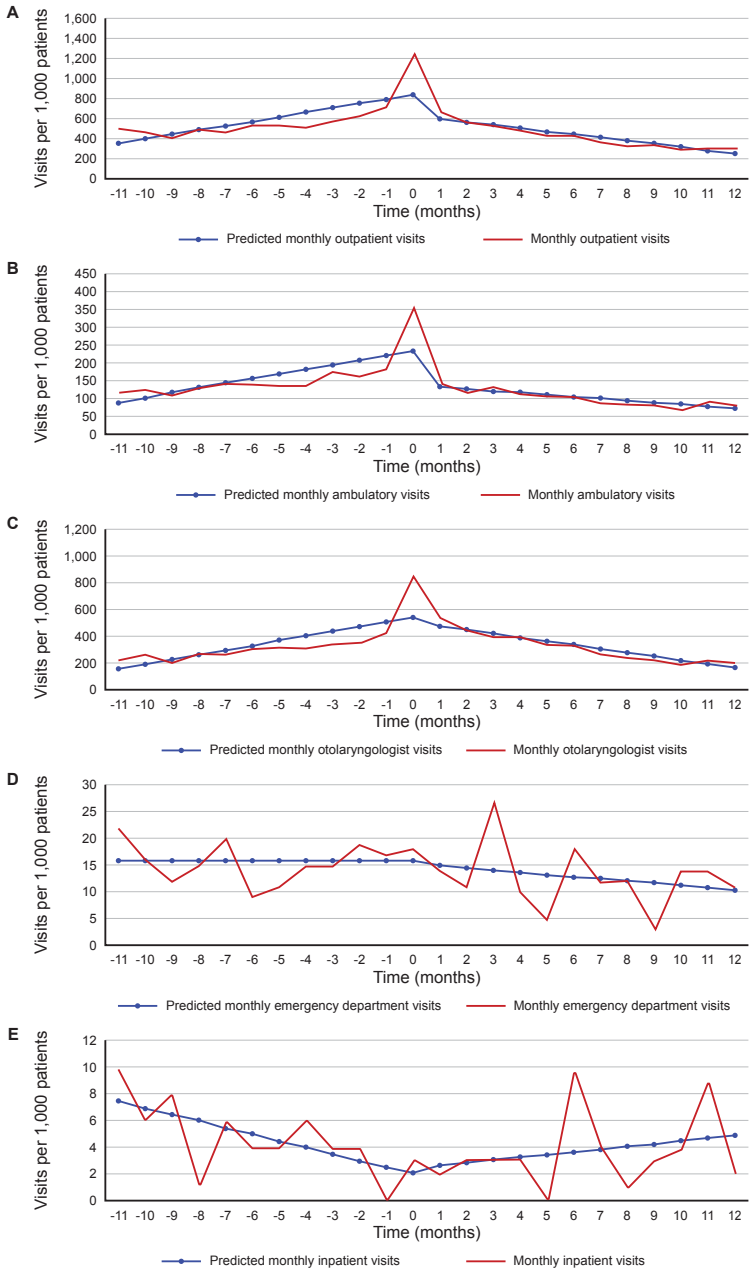

Figure 1. Trends over time for monthly (A) outpatient visits, (B) ambulatory visits, (C) otolaryngologist visits, (D) emergency visits, and (E) inpatient visits per 1,000 patients in the 12-month pre-dupilumab treatment (baseline) and in the 12-month post-dupilumab initiation (follow-up).

Similar results were observed for ambulatory (Figure 1B and Table S2) and otolaryngologist visits (Figure 1C and Table S2), with the exception that there was no change from the last observation before dupilumab initiation to the first observation after dupilumab initiation for otolaryngologist visits. There was no change in trend for emergency visits and inpatient visits (Figure 1D and 1E and Table S2).

Medication use during the follow-up period

Medication use during the follow-up period is shown in Table 3. The proportion of patients who used OCS for any reason decreased from 68.1% at baseline to 28.7% during follow-up (nominal $P < .001$), marking a 58% reduction. The proportion of patients with CRSwNP-related OCS use decreased from 59.1% at baseline to 17.7% during follow up (nominal $P < .001$), a 70% reduction. The cumulative number of CRSwNP-related OCS prescriptions/fills decreased from 553 during baseline to 132 during the follow-up period (nominal $P < .001$). A total of 316 (31.0%) patients used short courses of CRSwNP-related OCS during the baseline period compared with 143 (14.1%) during the follow-up period (nominal $P < .001$). Among patients who used short courses of CRSwNP-related OCS, the mean (SD) number of short courses

Table 3. Medication, procedures, and imaging during the baseline and follow up periods.

	Baseline (N = 1,016)	Follow-up (N = 1,016)	Nominal P value
Medications			
All-cause corticosteroids (any)	905 (89.1)	645 (63.5)	< .001*
Oral corticosteroids	692 (68.1)	292 (28.7)	< .001*
Prescription intranasal corticosteroids	513 (50.5)	316 (31.1)	< .001*
CRSwNP-related corticosteroids (any)			
Oral corticosteroids	600 (59.1)	180 (17.7)	< .001*
Cumulative number of prescriptions/fills	553	132	< .001†
Patients with short courses	316 (31.1)	143 (14.1)	< .001*
Number of short courses per patient, mean (SD)	1.5 (0.9)	1.2 (0.5)	< .001†
Antibiotics	656 (64.6)	323 (31.8)	< .001*
Procedures and imaging			
Nasal endoscopy	723 (71.2)	483 (47.5)	< .001*
CT	225 (22.1)	46 (4.5)	< .001*
MRI	0	1 (0.1)	.317*

All data are n (%), unless otherwise stated. CRSwNP, chronic rhinosinusitis with nasal polyps; CT, computed tomography; MRI, magnetic resonance imaging; SD, standard deviation. *Nominal P value calculated using Chi-square test. † Nominal P value calculated using Wilcoxon test.

per patient decreased from 1.5 (0.9) during the baseline period to 1.2 (0.5) during the follow-up period (nominal P < .001). Antibiotic use was lower during the follow-up period compared with baseline (31.8% vs 64.6%; nominal P < .001). Additionally, prescribed INCS decreased from 50.5% during the baseline period to 31.1% during the follow-up period (nominal P < .001). In the subgroup with coexisting asthma, the proportion of patients using CRSwNP-related OCS decreased from 58.7% during the baseline period to 18.7% during the follow-up period (not statistically tested).

AESIs in the safety cohort

The AESIs were assessed for all patients in the dupilumab cohort while on treatment, regardless of the length of their available linked data (EMR and claims) following dupilumab initiation (n = 2,101; safety cohort). The incidence of AESIs during the baseline period and after dupilumab initiation is shown in Table 4. The most frequently reported AESI was serious infection, reported in 3.5% of patients during the baseline period and 2.1% during the follow-up period.

Discussion

There is currently a lack of studies on the effectiveness of dupilumab in patients with CRSwNP in the US. This retrospective claims-based study assessed the real-world effectiveness of dupilumab on medication and HCRU in patients with CRSwNP who initiated dupilumab in US clinical practice.

The characteristics of patients initiating dupilumab for CRSwNP in our study are similar to those of the randomized clinical trials and real-world evidence from Europe and Canada [16,18,19,21,22], with a similar tendency toward a lower female-to-male ratio and a prevalence of asthma in more than half of the patients. However, in this US-based cohort, a smaller proportion of patients had a record of coexisting AERD compared with other studies [18,21,22]. This may be due to the absence of an International Classification of Diseases (ICD) code specific to this condition rather than a major difference in prevalence or diagnosis. Consistent with other real-world studies [19,21,22], our study showed that corticosteroid burden was high in the year preceding dupilumab initiation. Additionally, the number of otolaryngologist, outpatient, and ambulatory visits was high before dupilumab initiation, consistent with a difficult-to-treat population and a lack of adequate treatment options [5,24].

CRSwNP is associated with high economic burden in terms of healthcare visits and surgical procedures [5,25]. In the overall analysis cohort, the number of outpatient, otolaryngologist, and emergency departments visits per patient was lower during follow-up vs baseline. Additionally, the number of sinus-related procedures, including sinus-related CT scans, decreased in the year following dupilumab initiation. Given the nature of the data source, it is reasonable to assume that patients were under the care of an otolaryngologist during both baseline and follow-up, and as such the observed reduction is unlikely to be explained by a shift in care from an otolaryngologist to another specialty. However, the possibility of this type of confounding cannot be entirely excluded. These results are supported by real-world evidence on the use of biologics in patients with CRSwNP [26,27]. Further studies will be needed to quantify the reduction in cost

Table 4. Adverse events of special interest reported during the baseline and follow up periods (safety cohort).

Patients, n (%)	Baseline period* (N = 2,101) †	Follow-up period (N = 2,101)†
Serious infection	73 (3.5)	45 (2.1)
Epistaxis/nosebleed	33 (1.6)	25 (1.2)
Eosinophilia	28 (1.3)	17 (0.8)
Gastrointestinal ulcer or bleed	23 (1.1)	18 (0.9)
Herpes simplex virus infection	11 (0.5)	9 (0.4)
Conjunctivitis	7 (0.3)	9 (0.4)
Anaphylaxis	7 (0.3)	0
Pericarditis	1 (<0.1)	1 (<0.1)
Opportunistic infection	1 (<0.1)	2 (0.1)
Parasitic infection	0	0

All data are n (%), unless otherwise stated. * Includes the date of dupilumab initiation. † This analysis includes all patients in the dupilumab cohort while on treatment, regardless of the length of their available linked data after dupilumab initiation.

resulting from decreased HCRU.

Our study showed that in the year following dupilumab initiation, the proportion of patients using both overall and CRSwNP-related OCS decreased compared with the year before dupilumab initiation. This finding is consistent with results from clinical trials and real-world evidence from other regions [19,26]. The current study augments previous findings by showing that the number of prescriptions/fills for CRSwNP-related OCS and the proportion of patients with short courses of CRSwNP-related OCS decrease after initiation of dupilumab [19,26].

Patients with CRSwNP and coexisting asthma represent a difficult-to-treat subgroup, potentially requiring high cumulative doses of systemic corticosteroids [28]. Our study reported a decrease in INCS and antibiotic use in the year following dupilumab initiation in patients with CRSwNP. Additionally, a decrease in the use of OCS was observed in patients with CRSwNP and coexisting asthma following dupilumab initiation. These findings are consistent with a previous real-world study that also reported a reduction in corticosteroid (including INCS) and antibiotic use in the year following dupilumab initiation for patients with CRSwNP and coexisting asthma [28]. Taken together, the findings of reduced use of healthcare resources, corticosteroids, and antibiotics in the 12 months after initiating dupilumab indicate improved disease control and reduced incidence of exacerbations.

Capturing adverse effects in real-world studies is important, even in claims database studies, where the accuracy of the findings may not align with that of controlled clinical trials. In this real-world study, there was no marked increase in the incidence of AESIs after initiation of dupilumab. Notably, the proportions of patients who reported serious infections and eosinophilia were lower after dupilumab initiation compared with before dupilumab initiation. Clinical trial studies previously reported transient eosinophilia in dupilumab treated patients with CRSwNP. However, these transient increases in eosinophil counts were not associated with clinical outcomes or treatment efficacy [29].

There are limitations to this study that are inherent to the structure of the data. For example, diagnostic codes defining comorbidities (e.g. ICD code missing for AERD) and AESIs are likely to provide only approximations. Patients with atopic dermatitis, with other biologic use, and who had endoscopic sinonasal surgery in the year before and after dupilumab initiation were excluded from our analysis, which limits the generalizability of our findings to the overall population of patients initiating dupilumab for CRSwNP. The exclusion of patients with endoscopic sinonasal surgery was because there was initially an exploratory plan to compare a dupilumab cohort with a surgery cohort. Additionally, reasons for visits and treatment discontinuation are not available and limit data interpretation. There are also limitations inherent to retrospective study designs and in the secondary use of data, such as medications ordered (e.g. as documented in the EMR) and prescriptions filled (as documented in the claims data), which are proxies for actual consumption. To address the limitation of the potential for missing data on medications, prescription orders from EMR and pharmacy claims were included to represent a more complete picture of treatment patterns. Because prescription INCS does not capture over-the-counter INCS, estimates of use and change in INCS may not reflect an accurate picture of INCS use. Additionally, the retrospective pre-post design without a control cohort may make the analysis susceptible to regression to the mean and/or confounding by indication. Further, as dupilumab is often initiated during periods of high disease activity, the baseline cohort may represent an escalation phase of care, and the observed decline in HCRU and medication use may represent a transition to a maintenance phase, rather than a causal effect of dupilumab. Similarly, another limitation of this study is that several outcomes are provider-dependent measures that may not reflect objective disease control, and corticosteroid exposure was measured by prescriptions or short courses rather than cumulative dose, which limits interpretation of a steroid-sparing effect. As such, the observed reduction in intranasal corticosteroid use may reflect changes in care patterns rather than biologic disease modification. Despite these limitations, given the limited US-based evidence for the real-world effectiveness of dupilumab in CRSwNP, and in support of emerging data from the EU and Canada [18-22], this study provides important information for healthcare providers.

Conclusion

Patients with CRSwNP who initiated dupilumab 300 mg every 2 weeks demonstrated reduced use of healthcare resources, corticosteroids, and antibiotics during the 12 months following dupilumab initiation compared with the 12 months pre dupilumab. These findings suggest an association between dupilumab treatment and reductions in HCRU and medication use, and provide supportive evidence of the real-world effectiveness of dupilumab in clinical practice.

Abbreviations

AERD: Aspirin-exacerbated respiratory disease; AESI:Adverse event of special interest; CRS: Chronic rhinosinusitis; CRSwNP: Chronic rhinosinusitis with nasal polyps; CT: Computed tomography; EMR: Electronic medical records; EU: European Union; HCRU: Healthcare resource utilization; ICD: International Classification of Diseases; INCS: Intranasal corticosteroids; MRI: Magnetic resonance imaging; NP: Nasal polyps; OCS: Oral corticosteroids; SD: Standard deviation; SE: Standard error; USA: United States of America

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Author contributions

Conceptualization: MC; formal analy¬sis: MC; funding acquisition: MC; methodology: MC; writing-original draft: MC; writing-review and editing: JKH, SEL, ATP, ZS, SN, MC, AR, JL. All authors have read and agreed to the published version of the manuscript.

Conflict of interest

JKH is an advisory board member for AstraZeneca, Genentech, GlaxoSmithKline, Novartis, Regeneron Pharmaceuticals Inc., and Sanofi. SEL has received clinical trial funding from, and is an advisory board member for, AstraZeneca, Genentech, GlaxoSmithKline, and Sanofi, and is also an advisory board member for Novartis, Regeneron Pharmaceuticals Inc., and Sanofi. ATP has received research support from AstraZeneca, Insmed, Regeneron Pharmaceuticals Inc., and Sanofi, and is an advisory board member for AstraZeneca, Chiesi, Eli Lilly, GlaxoSmithKline, Regeneron Pharmaceuticals Inc., and Sanofi. ZS has received speaker fees from GlaxoSmithKline and Regeneron Pharmaceuticals Inc., is an advisory board member and/or consultant for Lyra, Novartis, Olympus, and Optinose, and is the Medical Director of Healthy Humming. SN and AR are employees of Regeneron Pharmaceuticals Inc. and may hold stock and/or stock options in the company. NK and MC are employees of Sanofi and may hold stock and/or stock options in the company. JL has received research funding from Regeneron Pharmaceuticals Inc. and Sanofi, and is an advisory board member and/or consultant for AstraZeneca, GlaxoSmithKline, Honeywell, Regeneron Pharmaceuticals Inc., and Sanofi.

Availability of data and materials

Qualified researchers may request access to the data and related study documents that support the findings of this study. Further details on Sanofi's data sharing criteria, eligible studies, and process for requesting access can be found at https://www.vivli.org.

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SUPPLEMENTARY MATERIAL

Table S1. Patient comorbidities.

	N = 1,016
Mean (SD) Charlson Comorbidity Index	0.9 (1.1)
Charlson Comorbidity Index category	
0–1	880 (86.6)
2–3	103 (10.1)
4–5	28 (2.8)
≥6	5 (0.5)
Type 2 inflammatory comorbidities*	
Allergic rhinitis	724 (71.3)
Asthma	579 (57.0)
AERD	20 (2.0)
Allergic conjunctivitis	17 (1.7)
Eosinophilic esophagitis	6 (0.6)
Other comorbidities†	
Diabetes	96 (9.4)
Chronic obstructive pulmonary disease	84 (8.3)
Rheumatoid arthritis	7 (0.7)
Psoriatic arthritis	4 (0.4)
Psoriasis	6 (0.6)
Crohn's disease	6 (0.6)
Ulcerative colitis	4 (0.4)

Data are n (%), unless otherwise stated. AERD, aspirin-exacerbated respiratory disease; SD, standard deviation. * Patients with atopic dermatitis were not included in this analysis. † Present in more than 1 patient (>0.1%).

Table S2. Results from segmented regression for monthly healthcare visits per 1,000 patients during the baseline and follow-up periods.

	Baseline estimate (SE)	Nominal P value
Outpatient visits		
Slope during baseline	43.9 (9.9)	< .001
Level change immediately after dupilumab initiation	-210.9 (97.3)	< .05
Slope during follow-up	-74.9 (14.0)	< .0001
Ambulatory visits		
Slope during baseline	13.1 (2.9)	< .001
Level change immediately after dupilumab initiation	-95.2 (28.3)	< .01
Slope during follow-up	-18.6 (4.1)	< .001
Otolaryngologist visits		
Slope during baseline	35.2 (7.4)	< .001
Level change immediately after dupilumab initiation	-38.4 (72.2)	.6007
Slope during follow-up	-63.8 (10.4)	< .0001
Emergency visits		
Slope during baseline	0.0 (0.4)	.9937
Level change immediately after dupilumab initiation	-0.5 (4.2)	.9029
Slope during follow-up	-0.4 (0.6)	.5094
Inpatient visits		
Slope during baseline	-0.5 (0.2)	< .05
Level change immediately after dupilumab initiation	0.4 (2.1)	.8370
Slope during follow-up	0.7 (0.3)	< .05

Nominal P value calculated using t-test. SE, standard error.