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Trends in dupilumab persistence among patients with chronic rhinosinusitis with nasal polyps*

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Abstract

Background: Establishing effective treatment algorithms for chronic rhinosinusitis with nasal polyps (CRSwNP) remains challenging, particularly concerning biologic therapies' discontinuation rates. Limited real-world data exist on the persistence of dupilumab, a biologic used in CRSwNP. We conducted a large-scale claims-based analysis to compare dupilumab discontinuation rates. **Methodology**: Utilizing the IBM MarketScan® Research Database, we identified CRS patients treated with dupilumab from July 2019 to December 2021. We assessed drug discontinuation rates, comorbidities, demographics, and surgical history using Kaplan-Meier curves and Cox proportional hazards models. **Results**: Of 1718 CRS patients on dupilumab, median age at initiation was 45 years, with 44% male. Dupilumab persistence varied by comorbidity, with patients with comorbid asthma exhibiting the longest median usage (652 days). Statistically significant differences in drug persistence were observed among comorbid conditions ($p<0.001$). Younger patients (<50 years) had higher discontinuation rates ($p<0.001$). **Conclusions**: Our study reveals that many CRS patients without comorbidities discontinue dupilumab within the first year, with a median duration of 366 days. Age and comorbidities significantly influence dupilumab persistence. These findings aid clinicians in counseling CRS patients and underscore the need for further research to optimize treatment strategies.

Key words: nasal polyps, quality of life, respiratory system, rhinitis, sinusitis

Introduction

Establishing biologic treatment algorithms for chronic rhinosinusitis with nasal polyps (CRSwNP) remains a challenge. Biologics require continuous usage, and discontinuation rates during routine clinical use of these costly therapies are poorly defined [(1)]. Few studies report discontinuation rates, and even fewer studies represent patients' interfacing with the US healthcare system.

In CRSwNP clinical trials, dupilumab discontinuation rates were low; in fact, discontinuation and adverse event rates were higher in the placebo groups [(2)]. European studies report low dupilumab discontinuation rates within the first year of therapy, ranging from 0%-16.05% [(3-6)], the largest of which was a phase IV study, reporting discontinuation rates of 3.24% (n=21/648) [(6)]. While discontinuation rates are low in industry-funded and European studies, few studies evaluate dupilumab discontinuation in the US.

One US-based study found that 25% of 99 patients did not use dupilumab persistently, with a median time to nonpersistance being 66 days. Of this cohort, 17% of the patients discontinued dupilumab [(7)]. Drug persistence refers to continuing treatment for the prescribed duration, defined as the interval between starting and discontinuing therapy [(8)]. Particularly in the US, cost and insurance pre-authorizations may impact persistence. Medication efficacy, tolerability, and side effects may also influence drug persistence. In light of this, we conducted a US insurance claims-based analysis to study dupilumab persistence in the CRSwNP patient population.

Methods

Data source

This IRB-approved claims-based study utilized the IBM MarketScan® Research Database to evaluate CRSwNP patients treated with dupilumab.

Table 1. Dupilumab persistence using index date to first medication gap greater than 45 days.

Covariate	n, (%)	Coefficient	HR	95% CI	p-value
Male Sex	757 (44%)	-0.12	0.89	0.78-1.01	0.08
Age > 50	568 (33%)	-0.24	0.78	0.68-0.90	**< 0.001**
No History of ESS	1,160 (68%)	0.13	1.14	0.99-1.31	0.07
Comorbidities					
AD	292 (17%)	(0.00)	(1.00)		
AD & Asthma	305 (18%)	-0.19	0.82	0.67-1.01	0.07
Asthma	885 (52%)	-0.40	0.67	0.56-0.80	**< 0.001**
None	236 (14%)	0.05	1.05	0.84-1.30	0.7

HR and 95% CIs were calculated using Cox proportional hazards model. Greater age was associated with an increased likelihood of persistence (HR=0.78, 95% CI 0.68-0.90; p<0.001). Comorbid asthma was associated with an increased likelihood of persistence (HR=0.67, 95% CI 0.56-0.80; p=<0.001). Sex did not significantly affect persistence. Abbreviations: ESS, functional endoscopic sinus surgery; AD, atopic dermatitis; HR, hazard ratio; CI, confidence interval.

Sample selection

Dupilumab was FDA-approved for CRSwNP June 16, 2019. This analysis queried MarketScan database for CRSwNP patients from July 1, 2019-December 31, 2021 (914 days). Included patients had at least two months of continuous enrollment before the index date and at least one year of follow-up data. Enrollees must have at least one of the following International Classification of Diseases (ICD) codes to be included in the CRSwNP group.

ICD codes:

- J33.0,471.0-Polyp of the Nasal Cavity
- J33.1,471.1-Polypoid sinus degeneration
- J33.8,471.8-Other polyp of sinus
- J33.9,471.9-Unspecified nasal polyp
- J32.0,473.0-Chronic Sinusitis Maxillary
- J32.1,473.1-Chronic Sinusitis Frontal
- J32.2,473.2-Chronic Sinusitis Ethmoidal
- J32.3,473.3-Chronic Sinusitis Sphenoidal
- J32.8,473.8-Other Chronic Sinusitis
- J32.9,473.9-Chronic Sinusitis, Unspecified

Patients were categorized as "End of Enrollment," which included patients who were no longer enrolled in the database and were therefore censored, or "Drug Discontinuation," patients who discontinued the drug and remained in the MarketScan database. Comorbid conditions, sex, age, and surgical history were extracted. Selection criteria details can be found in Supplemental Table1.

Statistical analysis

Persistence is the duration of drug use, measured by calculating the interval from the index date to the date of discontinuation [8,9]. Treatment discontinuation was defined as more than 45 days between the last day of supply and the next refill date. A right-censored Kaplan-Meier curve with a log-rank test and Cox proportional hazards models were used. Analyses were performed using RStudio (Version2023.06.0+421, RStudioInc., Boston, MA, USA).

Results

From July 2019 to December 2021, 1718 CRSwNP patients met the inclusion criteria. Of these, 558 (32.5%) had a history of sinus surgery. The mean follow-up was 617 days (SD=155), calculated as the interval between the index date and the end of enrollment. Patients were enrolled in the database for a mean of 2566 days (SD=1569). Prior to initiating dupilumab, patients were enrolled for a mean of 1278 days (SD=1308).

The median age at the time of drug initiation was 45 years (IQR=34-53), and 44% (757/1718) were male. Dupilumab persistence varied by comorbidity (Figure1). CRSwNP patients with comorbid asthma had the longest median drug usage (652 days, 95%CI=586-760), while CRSwNP patients without asthma or AD had the shortest median duration (366 days, 95%CI=301-431). A non-right-censored curve showed similar trends (Supplemental Figure1).

There were differences in dupilumab persistence when comparing comorbid conditions (log-rank test, p<0.001). At one year, dupilumab persistence was 50.03% for CRSwNP patients without comorbid conditions (95%CI=44.01-56.80), 53.77% (95%CI=48.34-59.80) for those with comorbid AD, 60.70% (95%CI=55.40-66.40) for those with comorbid AD and asthma, and 67.12% (95%CI=64.09-70.29) for those with comorbid asthma.

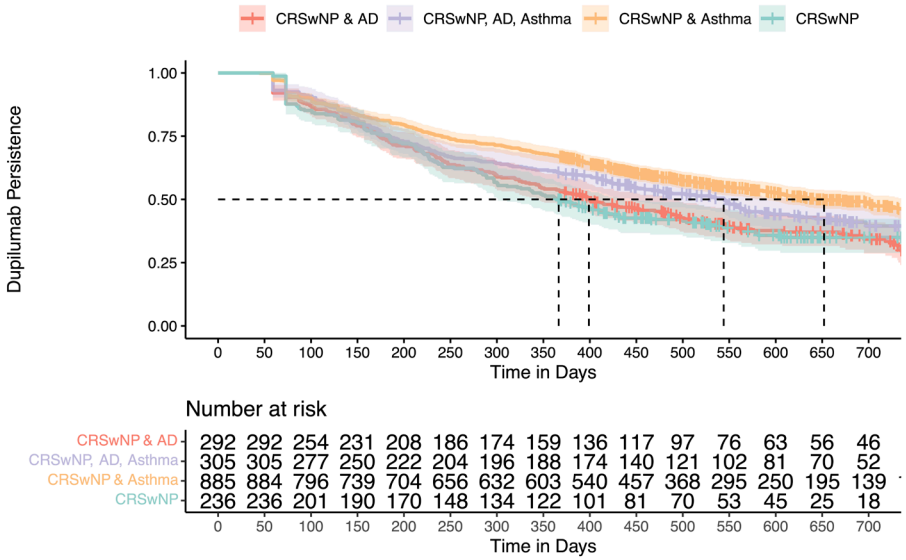

Figure 1. Duration of dupilumab use depends on comorbidities. Kaplan-Meyer survival curve representing median drug usage by comorbidity. The dotted line indicates median drug persistence. Those with no comorbidities had a median dupilumab use of 366 days (95% CI 301-431). For those with comorbid AD, median use was 399 days (95% CI 346-493). Median use was 544 days (95% CI 444-614) for those with both comorbid AD and asthma. For those with comorbid asthma, median use was 652 days (95% CI 586-760). Censored data is represented by tick marks. The log-rank test determined the differences in these drug survival curves to be statistically significant ($p < 0.001$). Abbreviations: AD, atopic dermatitis; CRSwNP, chronic rhinosinusitis with nasal polyps.

There were statistically significant differences in univariate HR (Table1). Those over 50 years were more likely to remain persistent (HR=0.78, 95%CI=0.69-0.90; p<0.001) and had a longer median drug use compared to those younger than 50 (627 days, 95%CI=546-748 vs. 488 days 95%CI=433-544; p<0.001). Those with comorbid asthma were more likely to remain persistent (HR=0.67, 95%CI=0.56-0.80; p<0.001).

Most patients on dupilumab had no documented history of endoscopic sinus surgery (ESS) (68%, 1160/1718), while 26% (443/1718) had one ESS, 4.9% (85/1718) had two ESS, and 1.7% (30/1718) had three or more ESS's before dupilumab initiation. Only 3.6% of patients underwent ESS after dupilumab discontinuation (61/1718), and 1.3% underwent ESS while on dupilumab (1.3%, 22/1718). Between 2019-2021, 44,749 CRSwNP patients in the database underwent ESS. Of those who underwent surgery, 1.25% (n=558/44,749) had previous or concurrent biologic use.

Discussion

Few real-world studies have investigated dupilumab use patterns in CRSwNP patients. Our data demonstrate that 50% of dupilumab users are nonpersistent within 366 days. These use patterns differ from previous studies, which cite low discontinuation rates over 12 months (Supplemental Table2) [3-6]. Our cohort of privately insured patients in the US, with a mean follow-up of 617 days, inherently differs from cohorts previously studied. In our cohort, dupilumab use patterns are likely influenced by cost, prior authorizations, insurance renewals, and changes in medications covered.

Despite EPOS guidelines recommending biologics for patients who had previously had surgery and have persistent bilateral polyps [10], our data demonstrate that most patients initiating dupilumab had no history of ESS (68%). Our sinus surgery data may be incomplete, as we only have patient data for the duration of their enrollment. The mean enrollment period before starting dupilumab was 1278 days, so any sinus surgeries that happened prior would not be included in our analysis.

Because dupilumab was FDA-approved for CRSwNP treatment in June 2019, the short timeline of this study limits our understanding of discontinuation rates. This study is also limited by the right-censored data. We cannot determine the specific cause of dupilumab discontinuation, though cost, lack of efficacy, and adverse events may be potential culprits.

Conclusions

Using data from a large claims-based dataset, we demonstrate that many CRSwNP patients without comorbidities discontinue dupilumab within the first year, and the median duration of dupilumab is 366 days.

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Authorship contribution

TS: Wrote manuscript and analyzed data; SZ: Wrote manuscript; TD, AM, BT, CKC, CE, BS: Assisted with editing of the manuscript; VP: Programmed the MarketScan data; AK: Wrote study protocol and assisted with data analysis and manuscript.

Ethics approval and consent to participate

This study was considered IRB-exempt by the Office of Human Research Ethics at UNC-Chapel Hill under IRB#22-2985.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

Conflict of interest

The authors declare that they have no competing interests.

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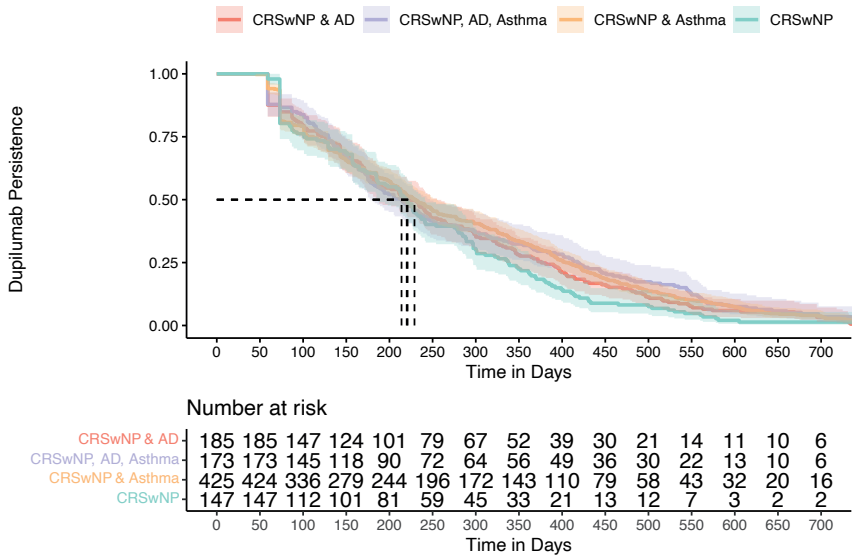
SUPPLEMENTARY MATERIAL

Supplemental Table 1. TITLE.

Type	Definition (example)
Sinus surgery codes used (CPT):	31253 - Nasal/sinus endoscopy, surgical with ethmoidectomy; total (anterior and posterior), including frontal sinus exploration, with removal of tissue from frontal sinus, when performed 31254 - Nasal/sinus endoscopy, surgical with ethmoidectomy; partial (anterior) 31255 - Nasal/sinus endoscopy, surgical with ethmoidectomy; total (anterior and posterior) 31256 - Nasal/sinus endoscopy, surgical, with maxillary antrostomy 31257 - Nasal/sinus endoscopy, surgical with ethmoidectomy; total (anterior and posterior), including sphenoidotomy 31259 - Nasal/sinus endoscopy, surgical with ethmoidectomy; total (anterior and posterior), including sphenoidotomy, with removal of tissue from the sphenoid sinus 31267 - Nasal/sinus endoscopy, surgical, with maxillary antrostomy; with removal of tissue from maxillary sinus 31276 - Nasal/sinus endoscopy, surgical, with frontal sinus exploration, including removal of tissue from frontal sinus, when performed 31287 - Nasal/sinus endoscopy, surgical, with sphenoidotomy; 31288 - Nasal/sinus endoscopy, surgical, with sphenoidotomy; with removal of tissue from the sphenoid sinus
Diagnosis codes used (ICD 9 and 10)	• J33.0, 471.0 Polyp of the Nasal Cavity • J33.1, 471.1 Polypoid sinus degeneration • J33.8, 471.8 Other polyp of sinus • J33.9, 471.9 Unspecified nasal polyp • J32.0, 473.0 Chronic Sinusitis Maxillary • J32.1, 473.1 Chronic Sinusitis Frontal • J32.2, 473.2 Chronic Sinusitis Ethmoidal • J32.3, 473.3 Chronic Sinusitis Sphenoidal • J32.8, 473.8 Other Chronic Sinusitis • J32.9, 473.9 Chronic Sinusitis, Unspecified

Supplemental Table 2. Studies with dupilumab discontinuation rates.

PMID	Author	n	Time-frame	Discontinuation rate	# Discontinued for > 60 days	Location/ Funding
37203259	Corso	648	12 mo.	3%	20	Italy
37948824	Gailetti	170	12 mo.	14%	24	Sicilian
37111387	Galletti	63	12 mo.	0%	3 were not adherent and were removed in the observation period	Italy
37394895	Lans	228	96 weeks	14%	31	Netherlands
37981023	Corey	99	Unknown	14%	14	US
37850768	Bellocchi	83	12 mo.	0%	0	Italy
31543428	Bachert	141	24 weeks		31/148 (Placebo), 13/147, 5/144	Industry Funded - SINUS-52
		291	24 weeks		9/130 (placebo), 4/141	Industry Funded - SINUS-24
37234094	Albrecht	81	12 mo.	16.05%	13	Germany
36654520	Trimarchi	21	6 mo.	0%	0	Italy
36242612	Jansen	40	13 mo.	5%	2	Germany



Supplemental Figure 1. Non-right censored KM curves demonstrating median drug persistence