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Real-world persistence with dupilumab among adults with atopic dermatitis

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ABSTRACT

Background: The real-world persistence with dupilumab therapy for atopic dermatitis (AD) is unknown.
Objective: To characterize adults with AD who initiated dupilumab and evaluate persistence with dupilumab therapy.
Methods: This retrospective cohort study used the IBM MarketScan Commercial and Medicare database. Adults with AD who initiated dupilumab (first dispensation = index date) between March 28, 2017, and March 31, 2018, were identified and followed up until September 30, 2018, or disenrollment. Twelve months of continuous preindex enrollment were required to characterize baseline treatment history and comorbidities. Kaplan-Meier analysis was used to estimate dupilumab persistence at 6 and 12 months, assuming a 14-day injection frequency and a 30-day grace period.
Results: A total of 1963 adults were identified who initiated dupilumab (mean [SD] age 42.1 [15.7] years; 50.7% women; 49.8% with ≥1 atopic comorbidity). Baseline AD treatments included topical corticosteroids (81.6%), systemic corticosteroids (72.5%), and systemic immunosuppressants (22.8%). Dupilumab persistence (95% confidence interval) at 6 and 12 months was 91.9% (90.7%-93.2%) and 77.3% (75.0%-79.7%), respectively. Among 329 patients who discontinued dupilumab, the risk of reinitiation was 78.8% (95% confidence interval: 75.8%-81.7%) within an average of 4 months.
Conclusion: Dupilumab persistence at 12 months was high, suggesting patient satisfaction with effectiveness, tolerability, and treatment regimen.

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Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease with a prevalence of 5% to 10% among adults in the United States, and approximately 4% among adults in Europe.[1,2] It is associated with up-regulation of type 2 immune responses (including those involving type 2 T-helper cells) and skin barrier dysfunction.[3-7] Clinical characterization includes the presence of pruritus (itch) and eczematous lesions, with itching, skin pain, and sleep and mental health disturbances among the most common patient complaints.[8-12] These symptoms have a profound impact on patients' lives, resulting in substantial patient-reported burdens across countries and cultures.[13-16]

Treatment guidelines recommend topical corticosteroids as first-line therapy. Although the use of systemic corticosteroids is generally discouraged,[17,18] there is potential value in the short-term use of systemic immunosuppressive agents for severe and refractory AD. However, systemic immunosuppressants have well-recognized safety issues, and their long-term use is not recommended.[17,19-24] Despite the historical availability of topical and systemic options, control of AD remains challenging, as suggested by studies that have reported inadequate control and its effects on patients.[25-28]

Dupilumab is a fully human monoclonal antibody that blocks interleukin (IL)-4Rα, resulting in inhibition of signaling by the IL-4Rα receptor ligands IL-4 and IL-13 that are key drivers of type 2 diseases.[29] Dupilumab was approved in the United States (Dupixent) in 2017 for adult patients with moderate to severe AD not adequately controlled with topical therapies or when those therapies are not advisable, and this was extended to pediatric patients aged 6 years and above.[30] It has also received marketing approval in the European Union for the treatment of moderate to severe AD in adolescent and adult patients who are candidates for systemic therapy.[31] These approvals were based on results from clinical trials that consistently found significant reductions vs placebo ($P < .05$) in clinical signs and symptoms and improvements in patient-reported outcomes including sleep and health-related quality of life[32-38]; long-term safety and efficacy have also been demonstrated.[39,40]

In routine clinical practice, long-term effectiveness is related to persistence on therapy, which is generally defined as "the duration of time from initiation to discontinuation of therapy."[41] Discontinuation of treatment may contribute to poor patient outcomes and increase health care resource utilization and costs,[42,43] but persistence itself may be dependent on both the effectiveness and tolerability of the drug. Although low rates of discontinuation were reported in dupilumab clinical trials (2.2%-11.5%),[33,36,39] patients enrolled in clinical trials may differ from real-world patients on factors affecting persistence (eg, disease severity and comorbidity burden); compliance monitoring procedures in trials may also result in higher persistence than in routine clinical practice. The objective of this study was to describe adult patients with AD who initiated treatment with dupilumab in a real-world setting and to assess their persistence on dupilumab.

Methods

Data Sources

The data sources for this retrospective observational cohort study were the 2016-2018 IBM MarketScan Commercial and Medicare supplemental databases. These data include longitudinal records of inpatient and outpatient services, long-term care, and prescription drug claims covered under a variety of fee-for-service and capitated health plans. Medical claims are linked to outpatient prescription drug claims and patient-level enrollment data through unique identifiers. The deidentified data are quality-controlled and compliant with the Health Insurance Portability and Accountability Act of 1996. Because the study did not contain individually identifiable data, institutional review board approval was not required.

Study Population

Patients who initiated dupilumab from March 28, 2017, through March 31, 2018, were identified; the first dupilumab dispensation was the index date. For inclusion in the analysis, patients were required to be at least 18 years old on the index date, with 1 or more International Classification of Disease, Tenth Revision (ICD-10) diagnosis codes for AD (L20.0, L20.81, L20.82, L20.84, L20.89, or L20.9) on or 12 months before the index date, and to have 12 months or more of continuous enrollment before the index date, which was defined as the baseline period. These patients were followed until the end of the study period (September 30, 2018) or disenrollment, whichever came first.

Dupilumab Exposure

Outpatient dispensations of dupilumab were identified using National Drug Codes (NDC). The duration of dupilumab treatment was estimated by assuming a 14-day injection frequency for each injection, as per the labeled prescribing information,[30] and allowing for a 30-day grace period between the estimated exposure end date and subsequent dispensation. Patients were assumed to have discontinued dupilumab if they did not have a dupilumab dispensation by the end of the 30-day grace period after the estimated exposure end date of their previous dupilumab dispensation. A subsequent dupilumab dispensation after discontinuation was considered a reinitiation.

Baseline Characteristics and Treatment History

Sociodemographic characteristics (age, sex, insurance status, and region) were categorized based on their value at the index date, and the presence of atopic comorbidities (allergic bronchopulmonary aspergillosis, allergic conjunctivitis, allergic rhinitis, alopecia areata, atopic keratoconjunctivitis, asthma, bullous pemphigoid, chronic rhinosinusitis, chronic spontaneous urticaria, eosinophilic esophagitis, eosinophilic gastroenteritis, food allergy, nasal polyposis, and prurigo nodularis) was identified based on ICD-10. The use of AD medications in the past year was identified using NDCs for outpatient dispensations and procedure codes for drug administration. These medications included topical corticosteroids stratified by potency (low, medium, high or very high), topical calcineurin inhibitors, topical phosphodiesterase-4 inhibitors, systemic corticosteroids (oral or injectable), phototherapy, and immunosuppressants (cyclosporine, azathioprine, mycophenolate, and methotrexate). NDCs were also used to identify past-year dispensations of pain medications (nonsteroidal anti-inflammatory drugs, opioids, analgesics, and other), sleep medications (antihistamines, benzodiazepines, sedatives and hypnotics, other), and other psychotropic medications (anxiolytics, antidepressants, and antipsychotics).

Statistical Analyses

Descriptive statistics were used to characterize demographics, comorbidities, and AD and non-AD treatments over the past year; counts and percentages are reported for categorical variables, and means and SDs are reported for continuous variables. Kaplan-Meier estimators, which take into account right-censoring, were used to determine treatment duration and persistence on dupilumab overall and at 6 and 12 months. The Hall-Wellner method was used to construct a 95% confidence band across the entire Kaplan-Meier survival curve,[44] because 95% confidence intervals (95% CIs) reflect point estimates and only provide survival probability at a single time point. A Kaplan-Meier approach was also used to estimate the risk of reinitiation and time to reinitiation among patients who discontinued

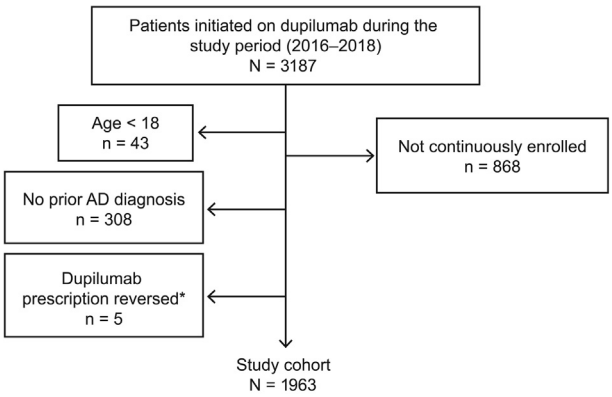

Figure 1. Study population flow chart. The asterisk symbol indicates that patient failed to pick up the medication. AD, atopic dermatitis.

dupilumab. To evaluate the robustness of the results, a sensitivity analysis was performed that allowed for a 45-day (vs a 30-day) grace period.

Analyses were conducted using the Instant Health Data platform (Boston Health Economics, Boston, Massachusetts) except for analyses using the Kaplan-Meier estimators, which were conducted using Statistical Analysis System software version 9.4 (SAS Institute, Cary, North Carolina).

Results

Population Characteristics

Among the 3187 patients in the database who initiated dupilumab between March 2017 and March 2018, 1963 met the study inclusion criteria (Fig 1). As shown in Table 1, the mean (SD) age was 42.1 (15.7) years; the patient population was evenly distributed between men (49.3%) and women (50.7%), and most patients were commercially insured (95.7%). Approximately half (49.8%) of the patients had 1 or more atopic comorbidity, with chronic spontaneous urticaria (37.8%), allergic rhinitis (34.7%), and asthma (26.5%) being the most prevalent atopic comorbidity (Table 1).

Treatment for AD was common during the baseline period and encompassed a variety of therapies (Table 1). Most patients were dispensed topical corticosteroids (81.6%), and more than half of patients who initiated dupilumab (50.3%) were dispensed high or very high potency topical corticosteroids during the baseline period. Furthermore, almost three-quarters (72.5%) of patients were dispensed systemic corticosteroids, and almost one-quarter (22.8%) used systemic immunosuppressants, of which exposure to cyclosporine (9.8%) and methotrexate (8.7%) was the most common (Table 1). The use of non-AD prescription medications was common—45.0%, 14.9%, and 54.1% were dispensed pain medications, sleep medications, and other psychotropic drugs (eg, anxiolytics, antidepressants, antipsychotics), respectively, over the baseline period (Table 1).

Persistence on Dupilumab

Patients initiating dupilumab were followed up on an average (SD) of 314.5 (128.4) days—during which patients received a mean (SD) of 8.6 (5.1) dupilumab dispensations from initiation to first discontinuation (Table 2). High rates of persistence were observed (Fig 2); at 6 and 12 months, persistence was 91.9% (95% CI: 90.7%-93.2%) and 77.3% (95% CI: 75.0%-79.7%), respectively (Table 2). Among the 329 patients who discontinued dupilumab therapy, the risk of reinitiation was 78.8% (95% CI: 75.8%-81.7%) within an average (SE) of 116.2 (4.8) days from the date of discontinuation (Table 2).

A sensitivity analysis that allowed for a 45-day grace period resulted in comparable persistence (Table 2). Persistence rates were 92.4% (95% CI: 91.2%-93.6%) at 6 months and 83.2% (95% CI: 81.2%-85.2%) at 12 months.

Discussion

This study used real-world data to characterize adults who initiated dupilumab therapy for AD and evaluated persistence with dupilumab in routine clinical practice. Characterization of the patient population before initiation of dupilumab showed that approximately half of the patients had at least 1 other atopic comorbidity, which is consistent not only with the burden of disease studies and dupilumab clinical trial populations but also with what may be expected based on the recognized association between AD and other atopic conditions.[39,45-48] A substantial proportion of patients with

Table 1
Demographic and Clinical Characteristics of the Patient Population at Baseline (N = 1963)

Variable	Value
Age, mean (SD), y	42.1 (15.7)
Sex, n (%)	
Male	967 (49.3)
Female	996 (50.7)
Insurance, n (%)	
Commercial	1878 (95.7)
Medicare	85 (4.3)
Geographic region, n (%)[a]	
Northeast	306 (17.7)
Midwest	328 (19.0)
South	750 (43.5)
West	342 (19.8)
Atopic comorbidities, n (%)	
Any atopic comorbidity	977 (49.8)
Chronic spontaneous urticaria	62 (37.8)
Allergic rhinitis	681 (34.7)
Asthma	521 (26.5)
Allergic conjunctivitis	131 (6.7)
Food allergy	132 (6.7)
Chronic rhinosinusitis	84 (4.3)
Prurigo nodularis	50 (2.6)
Alopecia areata	17 (0.9)
Atopic keratoconjunctivitis	11 (0.6)
Nasal polyps	8 (0.4)
Allergic bronchopulmonary aspergillosis	5 (0.3)
Eosinophilic esophagitis	3 (0.2)
Eosinophilic gastroenteritis	1 (0.1)
Bullous pemphigoid	0
AD treatments in past 12 mo, n (%)	
Topical corticosteroids[b]	1602 (81.6)
High or very high strength	987 (50.3)
Medium strength	1113 (56.7)
Low strength	402 (20.5)
Topical calcineurin inhibitors	532 (27.1)
Phosphodiesterase-4 inhibitor	331 (16.9)
Systemic (oral or injectable) corticosteroids	1423 (72.5)
Phototherapy	190 (9.7)
Immunosuppressants	447 (22.8)
Cyclosporine	193 (9.8)
Methotrexate	170 (8.7)
Mycophenolate mofetil	109 (5.6)
Azathioprine	38 (1.9)
Other medications in past 12 mo, n (%)	
Pain medications[c]	884 (45.0)
Sleep medications[d]	292 (14.9)
Other psychotropic drugs[e]	1062 (54.1)

Abbreviation: AD, atopic dermatitis.
[a]Data were missing on region for 237 (12.1%) patients.
[b]Percentage was greater than 100% because patients could be on different strengths during the baseline period.
[c]Includes nonsteroidal anti-inflammatory drugs, opioids, analgesics, and other.
[d]Includes antihistamines, benzodiazepines, sedatives and hypnotics, other.
[e]Includes anxiolytics, antidepressants, and antipsychotics (tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, benzodiazepines, other).

Table 2
Persistence With Dupilumab Treatment Over Follow-up

Variable	30-day grace period	45-day grace period
Duration of follow-up, d, mean (SD)	314.5 (128.4)	314.5 (128.4)
Number of dupilumab dispensations from initiation to discontinuation, mean (SD)	8.6 (5.1)	8.2 (4.6)
Dupilumab discontinuation, n	329	254
Dupilumab reinitiation, n	230	157
Risk of reinitiation, % (95% CI)	78.8 (75.8-81.7)	86.4 (84.1-88.6)
Time between discontinuation and reinitiation, d, mean (SE)	116.2 (4.8)	139.7 (6.2)
Persistence, % (95% CI)		
6 mo	91.9 (90.7-93.2)	92.4 (91.2-93.6)
12 mo	77.3 (75.0-79.7)	83.2 (81.2-85.2)
Overall	74.5 (71.6-77.4)	81.7 (79.4-84.0)

Abbreviation: CI, confidence interval.

AD also had a history of use of systemic corticosteroids or off-label use of nonsteroidal immunosuppressants, which is likely the result of the unmet clinical need among these patients. Nonsteroidal immunosuppressants, in particular, are associated with a low rate of persistence (31.5%) over 12 months and increased treatment burden arising from a need for monitoring because of their risk of adverse effects.[49] In addition to AD therapies, patients also had a history of use of pain medications, sleep medications, and other psychotropics. In AD, psychological distress can reach levels that are clinically relevant and may be so severe that drug treatment and even psychiatric hospitalization may be warranted.[50-55] Moreover, the use of these medications is likely related to sleep problems and pain, which are common complaints among patients with AD.[8,10,11]

Persistence on dupilumab in real-world clinical practice was high, with more than three-quarters of patients (77.3%) remaining on dupilumab at 12 months. These results were comparable when the length of the grace period was extended to 45 days; persistence at 12 months was 83.2%. A 30-day grace period represents a conservative approach to estimating persistence; a 45-day period has typically been used in studies of persistence with biologic agents for the treatment of psoriasis,[56] and 1 study permitted an 8-week gap for adalimumab,[57] which has a similar administration regimen as dupilumab (ie, every 2 weeks). Although discontinuations were uncommon, it should be noted that most patients (approximately 75%) who discontinued subsequently reinitiated treatment, on an average of less than 4 months after discontinuation.

For additional context, real-world 12-month persistence rates for approved biologic therapies for psoriasis tend to be lower than the 12-month persistence on dupilumab, although persistence varies by agent and frequency of administration.[56,57] For example,

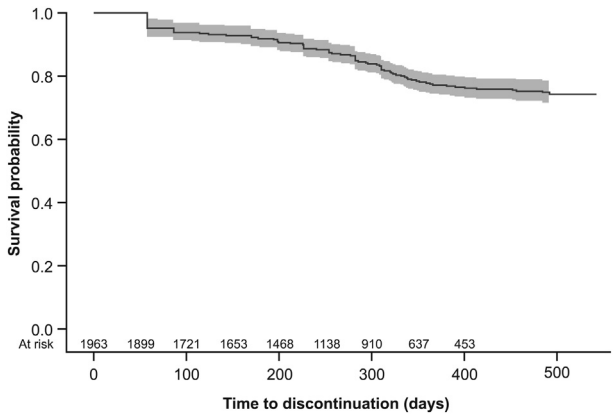

Figure 2. Persistence with dupilumab treatment allowing a 30-day grace period. Kaplan-Meier survival analysis was used to estimate persistence with dupilumab therapy. Blue shading represents the Hall-Wellner 95% confidence band.

12-month persistence on adalimumab, which is typically prescribed as a first-line treatment for psoriasis, was 50% to 62% across studies.[56,57] The highest persistence at 12 months was for ustekinumab (71%-81%), which is administered every 12 weeks. Infliximab, necessitating weekly administrations, had the lowest persistence (19%-50% at 12 months).[56,57] These findings suggest that persistence with dupilumab among patients with AD in the real-world may be higher than with biologic agents having a similar frequency of dosing for the treatment of psoriasis in routine clinical practice. Although it was not possible in this study to determine the reasons why patients discontinued dupilumab, discontinuation may be affected by the effectiveness and tolerability of treatment, the complexity of the drug administration regimen, and ability to obtain adequate insurance coverage.[58-60] A single-center study of 77 real-world patients who initiated dupilumab reported that treatment improved clinical disease severity over follow-up in 86% of patients and that 19 of the 77 patients (24.7%) discontinued treatment for a variety of reasons, including lack of effectiveness (6 of 19), adverse events (6 of 19), and insurance coverage (2 of 19).[61] However, it is unclear as to what extent the distribution of reasons for discontinuation is generalizable to this study, given that approximately 75% of patients in this study reinitiated dupilumab shortly after discontinuation.

Interpretation of the results of this study should consider the study limitations, such as the potential for misclassification of patients in claims-based analyses that rely on ICD diagnostic codes for population identification. The study population included only early initiators of dupilumab, which likely reflects more severe patients, potentially reducing generalizability because persistence may be different in a more diverse population of patients who initiate dupilumab. The duration of treatment and persistence was based on assumptions about whether and how patients take their treatment, and such assumptions may result in misclassification that could potentially over- or underestimate persistence. In addition, as previously noted, the reasons for discontinuation are unknown because such information is not available in claims databases. Similarly, the reasons why patients are persistent in dupilumab treatment can only be inferred. Finally, although the most recent data available were used, the ability to estimate persistence beyond 1 year was limited because dupilumab was newly launched.

In conclusion, the results from this real-world study of adults with AD reveal that those who initiated dupilumab therapy had a high prevalence of atopic comorbidities and past-year use of systemic corticosteroids, immunosuppressants, and non-AD medications. The use of pain, sleep, and other psychotropic medications was high, suggesting these patients experience comorbid conditions, including pain, anxiety, depression, and sleep disorders. Persistence with dupilumab therapy was high, and among the few patients who discontinued, more than three-quarters reinitiated treatment within 4 months. When comparing with 12-month persistence with biologics used to treat psoriasis, the high level of persistence with dupilumab at 12 months suggests that dupilumab is well tolerated and that patients are satisfied with its effectiveness and frequency of administration for the management of their AD. Additional studies are needed to confirm the real-world effectiveness of dupilumab through assessment of outcomes such as disease severity, health care resource use, and health-related quality of life, and to determine the reasons for the observed pattern of discontinuation and reinitiation. Such studies that characterize patients, treatment patterns, and outcomes in the clinical setting may help improve the management of AD.

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