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Original Article

Real-world impact of dupilumab on asthma disease burden in Japan: The CROSSROAD study

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ANCOVA, analysis of covariance;
 CI, confidence interval; COPD, chronic obstructive pulmonary disease;
 DPC, Diagnosis Procedure Combination;
 ICD10, International Classification of Diseases, 10th Revision; ICS, inhaled corticosteroid; IL, interleukin; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroid; RECORD, REporting of studies Conducted using Observational Routinely-collected health Data;
 SABA, short-acting beta agonist;
 SD, standard deviation; Q1, first quartile; Q3, third quartile

ABSTRACT

Background: Dupilumab, a human monoclonal anti-interleukin (IL)-4Ra antibody blocks the shared receptor component of IL-4 and IL-13, drivers of type 2 inflammation. Dupilumab is approved for severe/refractory asthma inadequately controlled by existing therapies, but knowledge of its effect on real-world disease burden is lacking. This study investigates real-world effects of dupilumab on asthma exacerbation risk and oral corticosteroid (OCS) use in Japanese individuals with asthma.

Methods: This retrospective, cohort study used a Japanese insurance claims database to identify patients who started dupilumab between 26 March 2019–31 May 2020. Patients were followed for ± 365 days from dupilumab initiation. The study primarily assessed the annual incidence rate of severe asthma exacerbations occurring simultaneously with hospitalizations or OCS bursts. Secondary and exploratory endpoints assessed OCS dosage and duration, and healthcare resource utilization (HRU), respectively.

Results: At dupilumab initiation ($N = 215$), mean age was 57.2 years, 41.9% of patients were aged ≥ 65 years, and 59.5% were female. Dupilumab significantly reduced the annual incidence of severe asthma exacerbations from 1.29 to 0.74 (95% confidence interval, 0.44–0.76) per patient per year. Mean OCS dosage decreased from 10.4 to 7.2 mg/day in chronic OCS users; median frequency of OCS bursts decreased from 3 to 0. Both unscheduled outpatient visits (35.8% vs 29.8%) and hospitalizations (21.9% vs 12.1%) decreased. Mean (standard deviation) duration of hospitalization also decreased from 6.7 (27.6) to 2.2 (8.1) days.

Conclusions: Japanese patients with asthma who received dupilumab had reduced incidence rates of severe asthma exacerbations, OCS use, and HRU over 12 months.

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Introduction

Asthma is characterized by chronic inflammation of the airways,^{1,2} and varies across individuals in terms of disease severity, progression and response to therapeutic drugs.^{2,3}

Globally, the prevalence of asthma ranges from 1% to 18%.⁴ Since the 1960s, the prevalence of asthma in Japan has increased from 1% in the general population to $\geq 10\%$ in children and to 6–10% in

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adults.⁵ In 2014, 1,177,000 Japanese patients with asthma visited hospitals and 103 per 100,000 required medical treatment.⁵

In recent years, the heterogeneity of asthma has become more apparent, such that it is no longer considered a single-entity disease.⁶ The most common type of asthma, type 2 inflammatory asthma, is mainly driven by T helper 2 cells and type 2 innate lymphoid cell activation.⁶ Biologic agents targeting inflammatory cytokines and immunoglobulins are largely used for type 2 inflammatory asthma that is severe; for example, the monoclonal antibodies omalizumab, mepolizumab, and benralizumab target immunoglobulin E, interleukin (IL)-5, and IL-5 receptor α , respectively.⁷ Another such biologic therapy is dupilumab, a human monoclonal anti-IL-4Ra antibody that targets the α -subunit of the anti-IL-4 receptor, thereby blocking IL-13 and IL-4 signaling pathways.⁸ Dupilumab is approved as add-on therapy in patients aged ≥ 12 years with severe or refractory asthma and whose symptoms are inadequately controlled with existing therapies in Japan,⁹ as add-on maintenance treatment in patients aged ≥ 6 years with moderate-to-severe asthma characterized by an eosinophilic phenotype or with oral corticosteroid (OCS)-dependent asthma in the United States,¹⁰ and as add-on maintenance treatment in patients aged ≥ 6 years with severe asthma with type 2 inflammation in Europe.¹¹ In the Japanese Asthma Prevention and Management Guidelines, dupilumab is included as an option in treatment steps 3 (for moderate and persistent asthma) and 4 (for severe and persistent asthma); OCS use is not mandatory at the initiation of dupilumab treatment.⁵

Previous clinical studies have demonstrated the efficacy and safety of dupilumab in individuals with moderate-to-severe or severe asthma.^{8,12,13} In the randomized Liberty Asthma QUEST study, dupilumab 200 mg or 300 mg every 2 weeks was associated with significantly lower severe asthma exacerbation rates, improved lung function, and better asthma control compared with placebo.¹² A subgroup analysis of the Liberty Asthma QUEST study showed that the efficacy and safety of dupilumab in Japanese patients with moderate-to-severe asthma was comparable with that observed in the overall study population.¹⁴ The OCS-sparing effects of dupilumab were demonstrated in the Liberty Asthma VENTURE study in patients with OCS-dependent severe asthma⁸; however, no Japanese patients were enrolled in this study. In a separate retrospective cohort study, OCS use among Japanese individuals with asthma was correlated with greater medical and economic burden, but confirmatory studies are required to complement these findings.¹⁵ Therefore, there is still limited information on the effects of dupilumab treatment on disease burden in those with severe asthma in routine clinical practice in Japan.

The current study investigated the effect of dupilumab on the risk of asthma exacerbations and OCS use in Japanese patients with asthma in a real-world setting.

Methods

Study design and patients

This was a retrospective cohort study conducted in patients with asthma (as determined by the International Classification of Diseases, 10th Revision [ICD10]: J45 or J46). Patients were identified from the Medical Data Vision health insurance claims and Diagnosis Procedure Combination (DPC) system database for acute-care inpatient hospital care (MDV database). As of August 2021, the MDV database contained insurance claim data from 449 hospitals (~11 million individuals per year), including information on diagnosis, drug prescriptions, medical procedures, laboratory values, patient characteristics, and disease severity. The personal data for each patient is anonymized, consistent with the Database Utilization

Committee of the Society of Clinical Epidemiology's principles for the use of large-scale medical databases to generate real-world evidence.¹⁶ Additionally, the MDV database distinguishes disease diagnosis and prescribed drugs using ICD10 codes and Anatomical Therapeutic Chemical codes, respectively.

Data from 1 January 2018 to 31 May 2021 were retrospectively extracted for patients who started dupilumab between 26 March 2019 and 31 May 2020. The date of dupilumab initiation during this time was defined as the index date and the start of follow-up while the observation period was defined as 365 days before and after the index date. The dupilumab treatment period was defined as the day after the index date to the latest date of dupilumab administration +14 days of follow up (to a maximum of 365 days).

The study included patients aged ≥ 12 years at the index date who had been diagnosed with asthma (ICD10: J45 or J46) in either an outpatient or inpatient setting; prescribed dupilumab at least once between 26 March 2019 and 31 May 2020; prescribed an inhaled corticosteroid (ICS) or long-acting beta-agonist (LABA) at least once before their first dupilumab prescription; and had ≥ 365 days of continuous enrolment before and after the index date.

The study protocol was approved by the institutional review board of the Shiba Palace Clinic (Tokyo, Japan; approval No. 149173_rn-32206 in 2022), and conducted in accordance with the Ethical Guidelines for Biomedical Research Involving Human Subjects, the ethical principles of the Declaration of Helsinki of 1965, and all relevant regulations applicable to non-interventional studies. Informed consent was waived as all personal information in the MDV database was anonymized. In addition, the study report has been prepared in accordance with the REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement.¹⁷

Study endpoints

The primary endpoint of this study was the incidence rate of severe asthma exacerbation (defined as per the ICD10 code J46 for status asthmaticus), occurring simultaneously with any of the following: an emergency department visit, hospitalization, intravenous corticosteroid injection, subcutaneous adrenaline injection, endotracheal intubation, ventilator use, or an OCS burst due to severe exacerbation of asthma. The annual incidence rate for the primary endpoint of severe asthma exacerbation was calculated by dividing the cumulative number of exacerbations by the cumulative patient-years before or during dupilumab treatment in the study cohort.

The secondary endpoints included: OCS burst, defined as prescription of OCS at an average daily prednisolone-equivalent dose of ≥ 20 mg for 1–14 days during an outpatient visit or a hospitalization due to asthma; and chronic OCS use, defined as prescription of OCS at an average daily prednisolone-equivalent dose of ≥ 5 mg for ≥ 180 days. Mean OCS dosage (in mg/day) was calculated as a prednisolone-equivalent dose from the sum of OCS doses and duration of use prior to starting dupilumab, the follow-up period, and each (30-day) evaluation period during follow-up. The prednisolone-equivalent OCS dosage was classified as follows: high-dose OCS: ≥ 10 mg/day; medium-dose OCS: >5 to <10 mg/day; low-dose OCS: ≤ 5 mg/day; or no OCS use. Duration of OCS use and mean OCS dosage calculated for overall OCS use were determined without distinction between an OCS burst and chronic OCS use. The ICS dose was classified as low-, medium-, or high-dose ICS according to the Japanese Asthma Prevention and Management Guidelines,^{5,18} where the ICS dose was derived from the prescription of ICS and maximum daily dosage indicated in the package insert.

Exploratory endpoints included: the effects of dupilumab treatment on the use of short-acting beta agonists (SABAs) during

an asthmatic attack (defined as prescription of SABAs in the same month as severe exacerbation) and on healthcare resource utilization (defined as unscheduled outpatient visits, such as after-hours, late-night and holiday visits, and hospitalization due to asthma exacerbation); and the effects of switching from other biologics to dupilumab on severe asthma exacerbation incidence and OCS dosage.

Statistical analysis

Descriptive statistics were used to present continuous variables, including mean, median, standard deviation (SD), first and third quartiles (Q1, Q3) and range (min–max), and categorical variables, including number and percentage. The ratio for the annual incidence rate before and during dupilumab treatment, and the 95% confidence interval (CI) for this ratio, were calculated using the Wald method. A generalized estimating equations model based on negative binomial data was used for the analysis, with log-transformed cumulative patient-years as an offset.

To evaluate the maintenance dosage, mean OCS dosage was evaluated in those with chronic OCS use prior to starting dupilumab. Percentage change from baseline in OCS dosage across periods was also calculated. Change in dosage from the day after dupilumab initiation to Days 331–365 was determined using analysis of covariance (ANCOVA), with use of biologics and OCS dose prior to

starting dupilumab as covariates. Change over time in OCS dosage during each 30-day evaluation period throughout the treatment was analyzed using descriptive statistics.

To determine chronic OCS use, the proportion of patients with a mean OCS dosage of ≤ 5 mg/day was calculated in the: (i) period prior to dupilumab initiation; (ii) each 30-day evaluation during treatment; and (iii) during the follow-up period. The number of OCS bursts from before and during dupilumab treatment were also analyzed for patients with and without chronic OCS use.

Subgroup analyses using important covariates related to asthma treatment, including biologic therapy and chronic OCS use prior to dupilumab initiation, were also performed for the primary and secondary endpoints.

Results

Patient characteristics

In total, 215 patients with asthma met all study inclusion criteria and were included in the study cohort (Fig. 1). At the index date, the mean (SD) age was 57.2 (19.5) years, 41.9% of patients were aged ≥ 65 years, and 59.5% were female (Table 1). According to medical database records, the most common asthma-related comorbidities were allergic rhinitis (71.2%), gastroesophageal reflux disease (62.8%), chronic obstructive pulmonary disease (COPD; 52.1%),

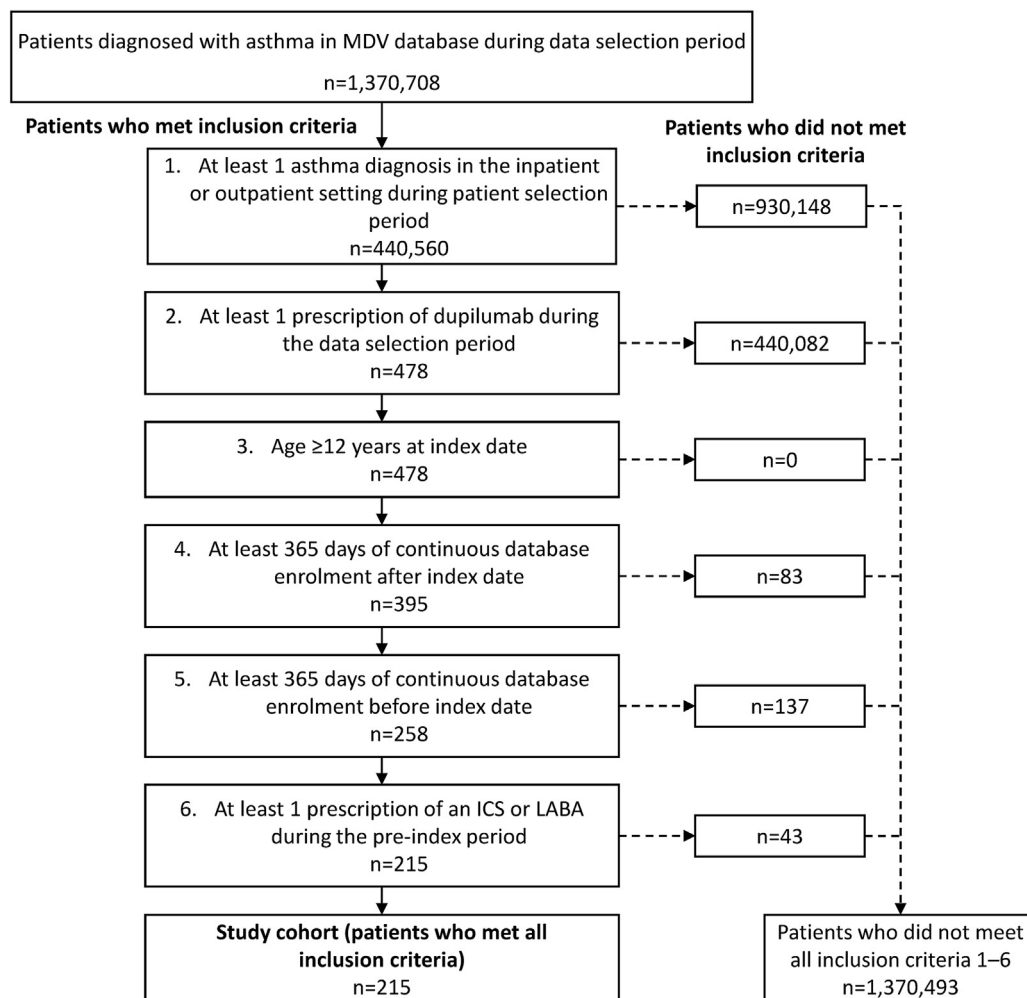


Fig. 1. Study patient flow. ICS, inhaled corticosteroid; LABA, long-acting beta-agonist.

Table 1
Selected baseline demographic and clinical characteristics for the study population.

Characteristic	N = 215
Age, years	
Mean (SD)	57.2 (19.5)
Range	12.0–98.0
Age ≥65 years, n (%)	90 (41.9)
Sex, n (%)	
Male	87 (40.5)
Female	128 (59.5)
Most common asthma-related comorbidities, n (%)	
Allergic rhinitis	153 (71.2)
Gastroesophageal reflux disease	135 (62.8)
Chronic obstructive pulmonary disease	112 (52.1)
Respiratory infections	75 (34.9)
Obstructive sleep apnea	72 (33.5)
Atopic dermatitis	61 (28.4)
Chronic sinusitis	59 (27.4)
Charlson Comorbidity Index	
Mean (SD)	2.7 (1.9)
Range	1.0–10.0
Most common Charlson comorbidities, n (%)	
Chronic pulmonary disease	215 (100.0)
Peptic ulcer disease	74 (34.4)
Congestive heart failure	51 (23.7)
Mild liver disease	33 (15.4)
Diabetes without chronic complications	30 (14.0)
Treatment during the year prior to dupilumab, n (%)	
Biologic agents	111 (51.6)
Benralizumab	35 (16.3)
Mepolizumab	35 (16.3)
Omalizumab	54 (25.1)
OCS	164 (76.3)
Chronic OCS	38 (17.7)
OCS burst	131 (60.9)
ICS (single agent)	40 (18.6)
LABA	210 (97.7)
Single agent	1 (0.5)
ICS/LABA	198 (92.1)
LAMA	123 (57.2)
Single agent	112 (52.1)
ICS/LABA/LAMA	11 (5.1)
High-dose ICS [†]	196 (91.2)
Medium-dose ICS [†]	18 (8.4)
Low-dose ICS [†]	1 (0.5)
SABA	142 (66.1)
LTRA	177 (82.3)
Theophylline	84 (39.1)
No OCS	51 (23.7)

ICS, inhaled corticosteroids; LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroids; SABA, short-acting beta agonist; SD, standard deviation.

[†] ICS (high-, medium-, and low-dose ICS) contain prescriptions of single-agent ICS, ICS/LABA and ICS/LABA/LAMA; high-, medium-, and low-dose ICS were defined according to the Japanese Asthma Prevention and Management Guidelines.^{5,18}

respiratory infections (34.9%), obstructive sleep apnea (33.5%), atopic dermatitis (28.4%), and chronic sinusitis (27.4%). The mean (SD) Charlson comorbidity index¹⁹ was 2.7 (1.9), and the most common Charlson comorbidities were chronic pulmonary disease (100.0%), peptic ulcer disease (34.4%), and congestive heart failure (23.7%; [Table 1](#)).

Prior to dupilumab initiation, 51.6% of patients had received biologics, 76.3% had received OCS, and 92.1% had received ICS/LABA therapy ([Table 1](#)). Pre-index biologic therapy included omalizumab in 54 patients (25.1%) and mepolizumab and benralizumab in 35 patients (16.3%) each. The majority of patients (91.2%) had received high-dose ICS, 43.7% of patients had received high-dose OCS (≥10 mg/day) during the pre-index period, and the mean (SD) duration of OCS treatment was 141.4 (138.1) days ([Table 2](#)).

Table 2

Dosage and duration of oral corticosteroid (OCS) therapy in the 12 months prior to starting dupilumab therapy.

	N = 215
OCS dose, n (%)	
High dose (≥10 mg/day)	94 (43.7)
Medium dose (>5 to <10 mg/day)	41 (19.1)
Low dose (≤5 mg/day)	29 (13.5)
Duration of OCS treatment, n (%)	
≥1 to ≤90 days	81 (37.7)
>90 to ≤180 days	17 (7.9)
>180 to ≤360 days	57 (26.5)
>360 days	9 (4.2)
Duration of OCS, days	
Mean (SD)	141.4 (138.1)
Median (Q1, Q3)	77.0 (18.0, 292.0)

OCS, oral corticosteroids; Q1, first quartile; Q3, third quartile; SD, standard deviation.

Overall, patients had a mean (SD) duration of dupilumab treatment of 297.8 (116.2) days.

Severe asthma exacerbations

The annual incidence rate of severe asthma exacerbation was significantly reduced from 1.29 per patient per year prior to dupilumab initiation to 0.74 per patient per year during the follow-up period, with a rate ratio of 0.58 (95% CI, 0.44–0.76) per patient per year ([Table 3](#)). The number of severe asthma exacerbations before and after starting dupilumab in the overall patient cohort is shown in [Supplementary Table 1](#).

In patients with chronic OCS use (n = 38), the annual incidence rate of severe asthma exacerbation was reduced from 2.21 to 1.07 per patient per year (rate ratio 0.49 [95% CI, 0.29–0.82]; [Table 3](#)). Patients with an OCS burst but without chronic OCS use (n = 102), also had a decrease in the annual incidence rate, from 1.73 to 0.97 per patient per year (rate ratio 0.56 [95% CI, 0.40–0.77]). In contrast, the annual incidence rate increased, from 0.16 to 0.30 per patient per year in patients who did not receive OCS prior to dupilumab initiation (n = 51), although the number of patients with severe exacerbation decreased from five to four.

In patients who received any biologics prior to dupilumab initiation (n = 111), the annual incidence rate of severe asthma exacerbation was reduced from 1.54 to 0.82 per patient per year (rate ratio 0.53 [95% CI, 0.38–0.74]; [Table 3](#)). Among patients previously treated with biologics, dupilumab reduced the annual incidence rate of severe asthma exacerbation from 1.85 to 0.84 (rate ratio 0.46, 95% CI 0.28–0.74) in those previously treated with omalizumab (n = 54), from 1.61 to 1.07 (rate ratio 0.66, 95% CI, 0.38–1.15) in those previously treated with mepolizumab (n = 35), and from 1.03 to 0.55 (rate ratio 0.53, 95% CI, 0.28–1.01) in those previously treated with benralizumab (n = 35).

Use of OCS

In patients with chronic OCS use (n = 38), the mean (SD) dosage of OCS decreased from 10.4 (5.4) mg/day prior to dupilumab initiation to 8.5 (5.5) mg/day during the follow-up period, and to 7.2 (6.1) mg/day in the last month of follow-up ([Fig. 2](#); [Table 4](#)). Compared with the pre-index period, this corresponded to a mean percentage reduction in OCS dosage of 29.0% and an adjusted percentage reduction of 31.8% (ANCOVA model).

The proportion of patients with an OCS dosage of ≤5 mg/day increased from 2.6% (n = 1) prior to dupilumab initiation to 39.5%

Table 3

Asthma exacerbations.

Asthma exacerbations	Number of events	Number of patients with events	Annual incidence rate, per patient per year (95% CI)	Rate difference, per patient per year (95% CI)	Rate ratio (95% CI)
All patients (n = 215)					
Prior to starting dupilumab	285	94	1.29 (1.01, 1.63)	—	—
During dupilumab treatment	130	52	0.74 (0.54, 1.02)	−0.55 (−0.82, −0.28)*	0.58 (0.44, 0.76)*
Patients who received other biologics prior to dupilumab (n = 111)					
Prior to starting dupilumab	178	54	1.54 (1.13, 2.11)	—	—
During dupilumab treatment	75	34	0.82 (0.57, 1.19)	−0.63 (−0.96, −0.30)**	0.53 (0.38, 0.74)**
Patients who did not receive any biologics prior to dupilumab (n = 104)					
Prior to starting dupilumab	107	40	1.01 (0.71, 1.44)	—	—
During dupilumab treatment	55	18	0.66 (0.38, 1.13)	−0.43 (−0.88, 0.02)	0.65 (0.41, 1.02)
Patients receiving chronic OCS prior to dupilumab (n = 38)					
Prior to starting dupilumab	83	20	2.21 (1.39, 3.51)	—	—
During dupilumab treatment	32	12	1.07 (0.59, 1.96)	−0.72 (−1.25, −0.20)†	0.49 (0.29, 0.82)†
Patients who received OCS (without chronic OCS) prior to dupilumab (n = 126)					
Prior to starting dupilumab	194	69	1.47 (1.13, 1.91)	—	—
During dupilumab treatment	86	36	0.82 (0.55, 1.20)	−0.59 (−0.91, −0.26)‡	0.56 (0.40, 0.77)‡
Patients who received an OCS burst (but without chronic OCS use) prior to dupilumab (n = 102)					
Prior to starting dupilumab	181	62	1.73 (1.34, 2.24)	—	—
During dupilumab treatment	83	34	0.97 (0.65, 1.44)	−0.58 (−0.91, −0.26)	0.56 (0.40, 0.77)§
Patients who did not receive OCS prior to dupilumab (n = 51)					
Prior to starting dupilumab	8	5	0.16 (0.06, 0.41)	—	—
During dupilumab treatment	12	4	0.30 (0.10, 0.91)	0.62 (−0.33, 1.58)	1.87 (0.72, 4.85)

CI, confidence interval; OCS, oral corticosteroids.

* P < 0.0001 vs prior to starting dupilumab.

** P < 0.0002 vs prior to starting dupilumab.

† P = 0.0068 vs prior to starting dupilumab.

‡ P = 0.0004 vs prior to starting dupilumab.

§ P = 0.0005 vs prior to starting dupilumab. P-values determined using the Wald method.

(n = 15) during the last month of follow-up; one patient discontinued chronic OCS use. Among those with chronic OCS use (n = 38), the median (Q1, Q3) frequency of OCS bursts decreased from 6.0 (2.0, 11.0) times prior to dupilumab initiation to 2.0 (1.0, 7.0) times after starting treatment.

In patients with an OCS burst but without chronic OCS use (n = 102), the median (Q1, Q3) frequency of OCS bursts decreased from 3.0 (2.0, 6.0) times prior to dupilumab to 0.0 (0.0, 2.0) times after dupilumab initiation; 52/102 patients (51.0%) did not receive an OCS burst for acute exacerbations following initiation of dupilumab.

Rescue therapy and healthcare resource utilization

The number of patients with a SABA prescription in the same month as an asthma exacerbation decreased from 86 (40.0%) prior to dupilumab initiation to 58 (27.0%) during the follow-up period. Additionally, the number of patients who needed three or more SABA prescriptions decreased from 65 (30.2%) to 42 (19.5%).

Patients with unscheduled outpatient visits decreased from 77 (35.8%) prior to dupilumab initiation to 64 (29.8%) during the follow-up period. Similarly, the number of patients with three or

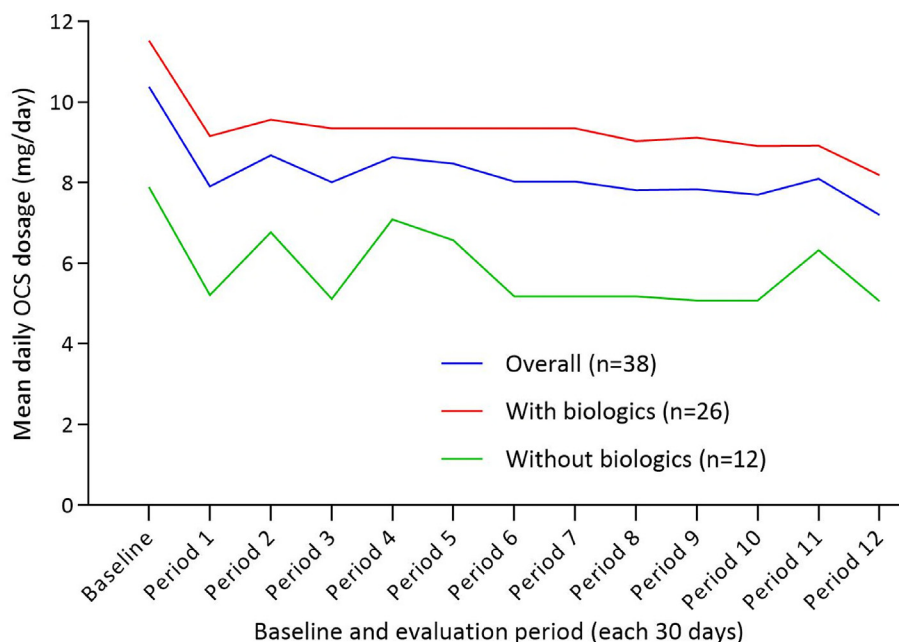


Fig. 2. Change in average daily oral corticosteroid dose over time following dupilumab treatment initiation. OCS, oral corticosteroid.

Table 4

Oral corticosteroid (OCS) dosage among patients who received chronic OCS prior to dupilumab (n = 38).

Period	Mean (SD) OCS dosage, mg/day	Mean (SD) % change in OCS dosage vs pre-index period	Patients achieving OCS dosage ≤ 5 mg/day, n (%)
Pre-index period	10.4 (5.4)	–	1 (2.6)
Follow-up period	8.5 (5.5)	–12.2 (44.6)	7 (18.4)
Period 1	7.9 (6.1)	–23.2 (47.5)	8 (21.1)
Period 2	8.7 (5.6)	–11.4 (46.6)	7 (18.4)
Period 3	8.0 (5.8)	–21.5 (41.6)	10 (26.3)
Period 4	8.6 (5.6)	–11.1 (46.7)	8 (21.1)
Period 5	8.5 (5.8)	–13.2 (50.5)	9 (23.7)
Period 6	8.0 (5.8)	–20.1 (43.2)	10 (26.3)
Period 7	8.0 (5.8)	–20.1 (43.2)	10 (26.3)
Period 8	7.8 (5.6)	–21.9 (44.6)	10 (26.3)
Period 9	7.8 (5.6)	–21.6 (43.2)	11 (29.0)
Period 10	7.7 (5.7)	–24.0 (46.2)	11 (29.0)
Period 11	8.1 (5.7)	–17.8 (51.4)	10 (26.3)
Period 12	7.2 (6.1)	–29.0 (49.9)	15 (39.5)

OCS, oral corticosteroids; SD, standard deviation.

more unscheduled visits also decreased after starting dupilumab, from 39 (18.1%) to 28 (13.0%) patients.

Overall, the number of patients requiring hospitalizations due to an asthma exacerbation decreased from 47 (21.9%) before dupilumab to 26 (12.1%) after starting dupilumab. Of these, the proportion of patients with one hospitalization decreased from 12.6% to 8.4%; patients with two hospitalizations decreased from 6.1% to 3.3%; and those with three or more hospitalizations decreased from 3.3% to 0.5% during the follow-up period. The mean (SD) duration of hospitalization was also reduced from 6.7 (27.6) to 2.2 (8.1) days.

Discussion

This is the first real-world study to focus on the impact of dupilumab on disease burden in Japanese patients with asthma. In our study, dupilumab was associated with a decrease in severe asthma exacerbations, OCS dosage, and reduced healthcare resource utilization over 12 months.

A previous claims data-based cohort study, which examined the impact of several biologic agents (benralizumab, dupilumab, omalizumab, and mepolizumab) on the disease burden in Japanese individuals with asthma, demonstrated that biologic therapy was associated with a reduction in asthma exacerbations and hospitalizations and had an corticosteroid-sparing effect.²⁰ In our study, we evaluated the impact of dupilumab on the incidence rate of severe asthma exacerbations and other components of the asthma disease burden. Dupilumab was associated with a 42% reduction in the incidence rate of severe asthma exacerbations, which was similar to reductions observed with dupilumab in previous studies, including a 14% rate reduction in the Japanese cohort study (rate ratio 0.86 [95% CI, 0.73–0.99])²⁰ and risk reductions of 48% (relative risk 0.52 [95% CI, 0.41–0.66]) and 46% (relative risk 0.54 [95% CI, 0.43–0.68]) with dupilumab 200 mg and 300 mg, respectively, in the randomized Liberty Asthma QUEST study.¹² However, comparisons between our study and these previous studies should be interpreted with caution due to differences in study design and population characteristics, with a higher proportion of dupilumab recipients in the previous real-world Japanese cohort study having comorbid atopic dermatitis (75%)²⁰ than in the current study (28%).

In subgroup analyses, the incidence rate of severe asthma exacerbations decreased during dupilumab treatment irrespective of prior biologic therapy. Although statistical significance was only shown in the subgroup of patients who received other biologics

prior to dupilumab, the number of exacerbations and the number of patients with exacerbations were reduced by half, indicating a clinically relevant effect of dupilumab, even in those who had no prior biologic therapy. One possible explanation for the lack of significant difference among the subgroup of patients with no prior biologic therapy is that the sample size was too small and the baseline exacerbation rate was too low to assess the effect of dupilumab on severe exacerbations in these patients. This subgroup had a lower annual incidence of severe exacerbations prior to starting dupilumab than other subgroups based on asthma treatment history, suggesting that patients in the biologic-naïve subgroup were prescribed dupilumab to control symptoms rather than to prevent exacerbations.

These findings add to those of previous real-world studies of dupilumab. In a Japanese retrospective study in 26 Japanese patients with severe asthma, dupilumab treatment led to a significant reduction in the incidence rate of annual exacerbations after a median follow-up of 12.6 months among those with prior biologic use (from 2.7 to 1.3 per patient per year; $p < 0.01$, $n = 16$), whereas the reduction in exacerbations did not reach significance in patients who had not previously received biologics.²¹ In another retrospective study of patients with inadequately controlled asthma, switching from other biologics (i.e., benralizumab, mepolizumab, or reslizumab) to dupilumab was associated with a significant reduction in median annualized exacerbations (by 0.81 per year) after 3–6 months of treatment, as well as improved lung function and increased asthma control.²² In clinical practice, this suggests that patients with poor asthma control may benefit from starting dupilumab treatment, particularly if other biologic therapy is ineffective.

In the subgroup of patients with chronic OCS use, dupilumab was associated with a 20.1% reduction in mean OCS dosage at Month 6 and 29.0% at Month 12 after dupilumab initiation. The reduction in cumulative OCS exposure is clinically relevant, as exposure to OCS and ICS has been associated with an increased risk of osteoporotic bone fractures in patients with asthma.²³ In the randomized VENTURE study, the percentage reduction in OCS dosage was 70.1% in the dupilumab group, although it is important to note that OCS dosage was adjusted down every 4 weeks according to a protocol pre-specified algorithm.⁸ Our study also demonstrated a reduction in the frequency of OCS bursts during dupilumab treatment. Of note, in patients receiving low-dose OCS (≤ 5 mg/day), it is likely that some patients represented cases where adrenal insufficiency may be latent due to long-term OCS use. In such cases, further reduction of OCS may be difficult.

In patients without OCS use before initiation of dupilumab, the annual incidence rate of severe asthma exacerbation increased from 0.16 to 0.30 per patients per year, although the number of patients with severe exacerbations decreased slightly. This rather unexpected finding was mainly influenced by one patient, who had an increase in the number of severe exacerbations from 2 before starting dupilumab to 7 after starting dupilumab. Of the four patients who showed a decrease in the number of exacerbations, three patients had a decrease in exacerbations from 1 to 0 and one patient had a decrease from 3 to 2 (Supplementary Table 2). However, due to the small number of patients in this subgroup, it would be difficult to draw conclusions about the efficacy of dupilumab in patients without OCS use, since it is also possible that these patients had a low risk of exacerbations at baseline and dupilumab may not have been needed to prevent exacerbations. These patients may have required optimization of their current asthma medication regimen, confirmation of treatment compliance, or additional therapies other than dupilumab. Although this study could not precisely monitor SABA use or OCS frequency, a decrease in SABA prescriptions and frequency of OCS bursts

suggests that dupilumab treatment reduced the incidence of mild to moderate exacerbations.

Our study showed a reduction in healthcare resource utilization during dupilumab treatment, as well as reductions in the incidence of unscheduled outpatient visits (from 35.8% to 29.8%), hospitalizations (from 21.9% to 12.1%), and the duration of hospital stays due to asthma exacerbation (from a mean of 6.7 to 2.2 days). Similarly, the previous Japanese cohort study showed a significant 52% reduction in the incidence rate of hospitalization due to asthma exacerbation with dupilumab (rate ratio 0.48 [95% CI, 0.33–0.69]).²⁰

There are several limitations to note for our study. Firstly, the MDV database utilizes administrative claims data and hospital discharge records; therefore, the data are subject to coding limits. Secondly, there is also a possibility of incomplete data for patients who may have transferred between hospitals. Thirdly, the database included individuals who were treated during inpatient hospitalization, as well as those treated in outpatient clinics, but could not track the history of visits to other hospitals. Since there are Japanese guidelines for dupilumab treatment,²⁴ it is unlikely that the use of this agent differs markedly between inpatient and outpatient settings. Fourthly, taking into account the study population's age (41.9% were ≥ 65 years of age), patients with COPD complications may have been included in the data set, which would have impacted the extent of reductions observed for the primary, secondary, and exploratory endpoints. Furthermore, the prevalence of the asthma-related comorbidity COPD may have been overestimated in the patient population as it was defined by codes J42, J43, and J44 with no supporting data on measured respiratory function. As there is no agreed definition of OCS burst, we defined this as administration of OCS at an average prednisolone-equivalent daily dose of ≥ 20 mg for 14 days. The GINA 2022 report states that the usual duration of OCS use for acute exacerbations in adults is 5–7 days,⁴ but previous database research used a definition of an average prednisolone-equivalent daily dose of ≥ 20 mg for 3–28 days.²⁵ Based on the fact that dose tapering is required if OCS treatment exceeds 2 weeks,⁴ we chose a treatment duration of 14 days for our definition of an OCS burst. However, in the absence of an agreed definition, it is possible that our analysis overestimated the incidence of OCS bursts by including some patients with chronic OCS use. Lastly, this study may have included patients who were prescribed dupilumab for conditions other than their asthma diagnosis, including atopic dermatitis and chronic sinusitis with nasal polyps. However, even if patients were prescribed dupilumab for atopic dermatitis, our results indicate that there is a beneficial effect on severe asthma exacerbations in patients with co-existing type 2 inflammatory conditions.

In conclusion, this real-world study of Japanese patients with asthma showed that dupilumab reduces the incidence rate of severe asthma exacerbations, OCS use, and healthcare resource utilization over 12 months of treatment.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.alit.2023.04.001>.

Conflict of interest

KF received honoraria from AstraZeneca, Boehringer Ingelheim, Novartis, GlaxoSmithKline, and Sanofi and research funding from Nippon Boehringer Ingelheim, Taiho Pharmaceutical, and Sanofi. ET received honoraria from AstraZeneca, Nippon Boehringer Ingelheim, Novartis, GlaxoSmithKline, Sanofi and Kyorin Pharmaceutical, and research funding from Nippon Boehringer Ingelheim and Taiho Pharmaceutical. MI, YS, and RK are employees and shareholders of Sanofi. AY received honoraria from AstraZeneca, Boehringer Ingelheim, Novartis, GlaxoSmithKline, and Sanofi.

Authors' contributions

All authors contributed to the study conception and design. MI, YS, and RK contributed to data analysis. All authors contributed to data interpretation, provided critical feedback during manuscript development, and approved the final manuscript.

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