Baseline Characteristics of Dupilumab-Treated Patients with Asthma in the Real World

The RAPID Global Registry

Lugogo, Njira L.; Soler, Xavier; Gon, Yasuhiro; Côté, Andréanne; Hilberg, Ole; Xia, Changming; Zhang, Yi; de Prado Gómez, Lucía; Rowe, Paul J.; Radwan, Amr; Jacob-Nara, Juby A.; Deniz, Yamo; Peters, Anju T.

Published in:
Advances in Therapy

DOI:
10.1007/s12325-024-03051-0

Publication date:
2025

Document version:
Final published version

Citation for pulished version (APA):
Lugogo, N. L., Soler, X., Gon, Y., Côté, A., Hilberg, O., Xia, C., Zhang, Y., de Prado Gómez, L., Rowe, P. J., Radwan, A., Jacob-Nara, J. A., Deniz, Y., & Peters, A. T. (2025). Baseline Characteristics of Dupilumab-Treated Patients with Asthma in the Real World: The RAPID Global Registry. *Advances in Therapy*, *42*(2), 849-862. Article 969243. https://doi.org/10.1007/s12325-024-03051-0

Adv Ther (2025) 42:849–862
https://doi.org/10.1007/s12325-024-03051-0

ORIGINAL RESEARCH

Baseline Characteristics of Dupilumab-Treated Patients with Asthma in the Real World: The RAPID Global Registry

Njira L. Lugogo · Xavier Soler · Yasuhiro Gon · Andréanne Côté · Ole Hilberg · Changming Xia · Yi Zhang · Lucía de Prado Gómez · Paul J. Rowe · Amr Radwan · Juby A. Jacob-Nara · Yamo Deniz · Anju T. Peters

Received: June 19, 2024 / Accepted: October 23, 2024 / Published online: December 9, 2024

ABSTRACT

Introduction: Patients with uncontrolled, moderate-to-severe asthma have a higher risk for exacerbations, negatively impacting lung function and quality of life. Dupilumab, a fully human monoclonal antibody, blocks interleukins 4 and 13, key and central drivers of type 2 inflammation. Dupilumab has been effective in the treatment of certain types of moderate-to-severe asthma across several clinical trials. We describe the characteristics of patients enrolled in RAPID, a global prospective registry, who initiated dupilumab (primary indication: asthma) in a real-world clinical setting.

Methods: A total of 205 patients (aged ≥ 12 years) were enrolled between March 2020 and October 2021 and are included in this analysis. Data are shown as mean (SD) unless stated otherwise.

Results: Patients were aged 50.1 (17.4) years and were mostly female (65.4%) and white (74.1%). At enrollment, 24.4% reported being current/former smokers and 86.8% had moderate-to-severe asthma (Global Initiative for Asthma steps 3–5). A mean (SD) of 4.4 (6.4) severe asthma exacerbations were reported in the year before enrolling in the registry in 78 of 152 patients with available data. Patients had reduced lung function [pre-bronchodilator forced expiratory volume in 1 s (FEV_1): 2.3 (1.1) L; pre-bronchodilator percent predicted

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12325-024-03051-0.

N. L. Lugogo (✉)
University of Michigan Medical School, 300 North Ingalls Street, Suite 2C40, Ann Arbor, MI 48109, USA
e-mail: nlugogo@med.umich.edu

X. Soler · C. Xia · Y. Zhang · A. Radwan · Y. Deniz
Regeneron Pharmaceuticals Inc., Tarrytown, NY, USA

Y. Gon
Nihon University, Tokyo, Japan

A. Côté
Quebec Heart and Lung Institute, Laval University, Quebec City, QC, Canada

O. Hilberg
Lillebaelt Hospital, Vejle, Denmark

L. de Prado Gómez
Sanofi, Madrid, Spain

P. J. Rowe · J. A. Jacob-Nara
Sanofi, Bridgewater, NJ, USA

A. T. Peters
Northwestern University Feinberg School of Medicine, Chicago, IL , USA

FEV_1: 70.3 (20.3) %] and poor asthma control [6-item Asthma Control Questionnaire: 2.4 (1.2); Asthma Quality of Life Questionnaire: 4.1 (1.3)]. The median (Q1–Q3) blood eosinophil count was 305 (200–695) cells/μL and the mean (SD) fractional exhaled nitric oxide levels were 42 (35) ppb (range: 4–186 ppb).

***Conclusion*:** Our findings suggest that most patients who enrolled in RAPID and initiated dupilumab in real-world clinical settings had a high disease burden, despite receiving current standard-of-care treatment at enrollment.

PLAIN LANGUAGE SUMMARY

Severe asthma can be difficult to control with currently available medicines. Asthma attacks, also called asthma flare-ups or exacerbations, are episodes where symptoms such as coughing, wheezing, shortness of breath, or chest tightness can suddenly occur or worsen, severely affecting quality of life. Dupilumab is a prescription medication used, along with other medicines, to treat asthma. In clinical trials, dupilumab worked well in patients with moderate-to-severe asthma, reducing the number of asthma attacks and improving lung function, characterized by easier breathing. To determine how well dupilumab works outside of a clinical trial setting, we look at studies set in the real world (observational studies). The RAPID registry is an observational study in which adolescents and adults starting dupilumab treatment for asthma are monitored by their doctor. Here, we report information on the first 205 patients who enrolled in the RAPID study between March 2020 and October 2021. At the beginning of the study, doctors diagnosed most patients (87%) with moderate-to-severe asthma. More than half of the patients had at least one severe asthma attack in the previous year but many had more than one (average: 4.4 attacks). Overall, patients had poor lung function, asthma control, and quality of life. Many patients also showed increased levels of markers for type 2 inflammation, an immune response activating cells such as eosinophils, mast cells, and T-cells. Overall, most patients with asthma who started dupilumab in a real-world clinical setting had a high disease burden, despite receiving standard-of-care treatment at the time of enrollment.

Keywords: Asthma; Asthma control; Disease burden; Dupilumab; Lung function; Real-world; Registry

Key Summary Points

Patients with uncontrolled, moderate-to-severe asthma have a higher risk for exacerbations, negatively impacting lung function and quality of life.

Dupilumab, a fully human monoclonal antibody which blocks interleukins 4 and 13, key and central drivers of type 2 inflammation, has been shown to be effective in the treatment of moderate-to-severe asthma in clinical trials.

This analysis describes the characteristics of patients enrolled in RAPID [Registry of Asthma Patients Initiating DUPIXENT® (NCT04287621)], a longitudinal prospective study designed to characterize adult and adolescent patients initiating therapy with dupilumab in real-world clinical practice for their asthma and to assess the long-term effectiveness and safety of dupilumab for the treatment of asthma in a clinical setting.

At enrollment in RAPID, patients had poor asthma control, reduced lung function, high exacerbation rates, and elevated biomarkers of type 2 inflammation in asthma.

These findings suggest that most patients who enrolled in RAPID and initiated dupilumab in real-world clinical settings had a high disease burden, despite receiving current standard-of-care treatment at enrollment.

INTRODUCTION

Asthma management goals include reducing exacerbations, improving lung function, and maximizing control of symptoms, resulting in a positive impact on patient quality of life (e.g., increasing activities of daily living or improved quality of sleep) and a decrease in the risk of asthma-related deaths [1]. Although asthma can be controlled in some patients with standard-of-care inhaled medications, including inhaled corticosteroids (ICS) and bronchodilators, [2] in many patients, it remains uncontrolled, [3] with asthma-related symptoms and exacerbations increasing the risk of reduced lung function.

Asthma is a chronic inflammatory disease affecting the lower airway. It has been demonstrated that 50–70% of patients with asthma have type 2 inflammation, characterized by elevated type 2 biomarkers, including blood eosinophils and fractional exhaled nitric oxide (FeNO) [4–6]. Biologic therapy has significantly advanced asthma treatment, and it has been recommended by the Global Initiative for Asthma (GINA) for patients with moderate-to-severe asthma and type 2 inflammation with exacerbations or persistence of symptoms while receiving high-dose ICS therapy [1].

Real-world evidence studies such as registries complement randomized clinical trials by providing information on patient populations outside of the tightly selected populations included in clinical trials [7]. Randomized clinical trials often have strict inclusion and exclusion criteria and may limit comorbid diseases. Therefore, despite being crucial in the development of new drugs, clinical trials may not fully represent clinical scenarios following drug approval [7]. Registry studies can provide additional insights into therapeutic effectiveness, safety, and other variables encountered in clinical practice.

Dupilumab, a fully human monoclonal antibody, [8, 9] blocks the shared receptor component for interleukin-4 and interleukin-13, which are key and central drivers of type 2 inflammation [10, 11]. In previous dupilumab asthma studies (phase 2b, phase 3 QUEST, phase 3 VENTURE, and open-label extension TRAVERSE), dupilumab significantly reduced the risk of severe asthma exacerbation and improved pre-bronchodilator forced expiratory volume in 1 s (FEV_1) in the overall population of patients with uncontrolled, moderate-to-severe asthma [12–15].

RAPID (Registry of Asthma Patients Initiating DUPIXENT® [NCT04287621)] is a longitudinal prospective study with the objectives of characterizing adult and adolescent patients initiating therapy with dupilumab in real-world clinical practice for their asthma and assessing the long-term effectiveness and safety of dupilumab for the treatment of asthma in a clinical setting. Here, we report the baseline demographic and disease characteristics of a large sample of adolescent and adult patients initiating dupilumab from March 2020 to October 2021 in a real-world clinical setting.

METHODS

Study Design

RAPID (NCT04287621) is a large, multi-country, longitudinal, prospective registry study [16] (Fig. 1). At the time of this analysis, 47 sites were participating in this study from the USA (including Puerto Rico), Denmark, and Sweden. The selection of participating sites attempted to capture a representative sample of patients who receive treatment with dupilumab in a real-world setting. Enrollment for the full registry will be approximately 700 patients (selected empirically, within the typical range of other registry studies, considering an estimated drop-out rate of approximately 15% per year).

Only countries where dupilumab has been approved and is commercially available were considered for participation. RAPID is being conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonisation Good Clinical Practice guideline, and applicable regulatory requirements. The RAPID protocol was reviewed and approved by the respective institutional review boards before patient recruitment. All patients provided written informed consent. For patients under the age

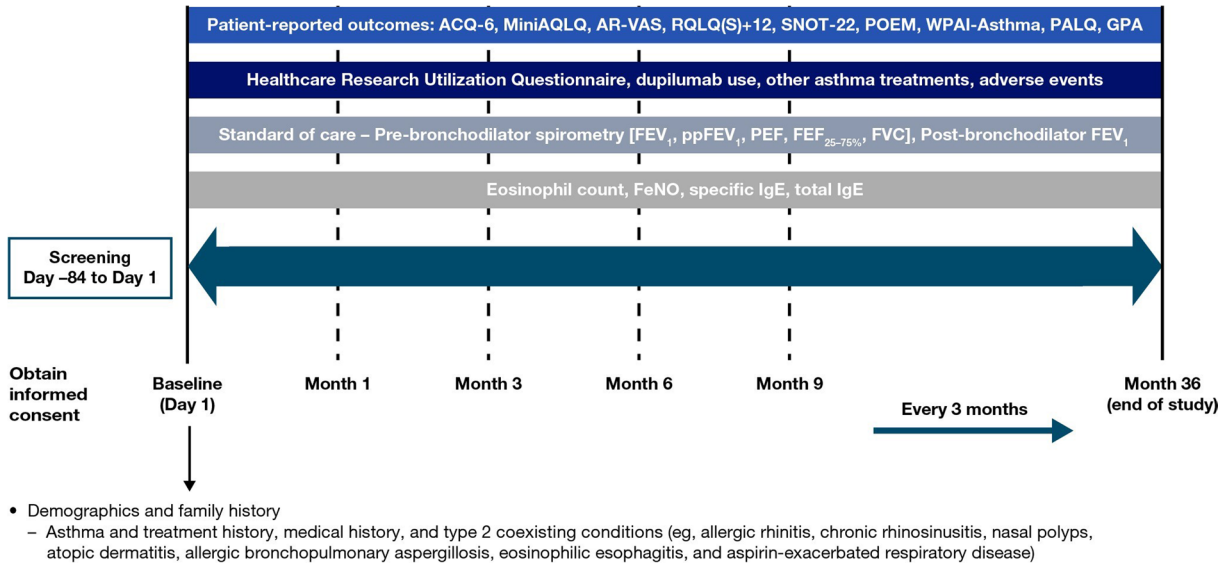

Fig. 1 RAPID study schedule of events and procedures (adapted from Gall R et al., 2023[16]). *ACQ-6* 6-item Asthma Control Questionnaire, *AR-VAS* Allergic Rhinitis Visual Analog Scale, *FeNO* fractional exhaled nitric oxide, $FEF_{25-75\%}$ forced expiratory flow between 25 and 75% of vital capacity, FEV_1 forced expiratory volume in 1 second, *FVC* forced vital capacity, *GPA* Global Patient Assessment, *IgE* immunoglobulin E, *Mini-AQLQ* Mini Asthma Quality of Life Questionnaire, *PALQ* Physical Activity Limitation Questionnaire, *PEF* peak expiratory flow, *POEM* Patient-Oriented Eczema Measure, $ppFEV_1$ percent predicted FEV_1, *RQLQ(S)+12* Standardized Rhinoconjunctivitis Quality of Life Questionnaire ≥ 12 years, *SNOT-22* 22-item Sino-Nasal Outcome Test, *WPAI-Asthma* Work Productivity and Activity Impairment Questionnaire for Asthma

of 18 years, both parental/legal guardian consent and patient assent were required.

Patients

The patients included in this analysis were enrolled in the registry between March 2020 and October 2021. The registry protocol was developed to allow for standard-of-care treatment and not interfere with normal clinical practice. Patient inclusion criteria were: age ≥ 12 years at the time of enrollment; initiating treatment with dupilumab for a primary indication of asthma according to the country-specific prescribing regulation; willing and able to comply with the required clinic visits, study procedures, and assessments; able to understand and complete study-related questionnaires; and able to provide signed informed consent.

Exclusion criteria were: those with a contraindication to dupilumab according to the country-specific prescribing requirement; treatment with dupilumab within 6 months before the screening visit, or within 6 months of the baseline visit if the screening and baseline visits occur on the same day; and any condition that, in the opinion of the investigator, might interfere with the ability to participate in the study.

Assessments

Data collected at baseline included demographics and disease characteristics such as severe asthma exacerbations in the previous year [defined as a worsening of asthma leading to ≥ 3 days of treatment with systemic corticosteroids (SCS), hospitalization, or emergency department visit leading to treatment with SCS] [17]. Medical history, asthma, and type 2 inflammatory comorbidity history, and asthma and non-asthma medications were recorded. Other assessments were: spirometry; FeNO; total and

specific immunoglobulin E (IgE); blood eosinophil count; Healthcare Resource Utilization Questionnaire; 6-item Asthma Control Questionnaire [ACQ-6; minimal clinically important difference (MCID) = 0.5] [18, 19]; Mini Asthma Quality of Life Questionnaire (MCID = 0.5) [20]; Allergic Rhinitis Visual Analog Scale (AR-VAS); Patient-Oriented Eczema Measure (POEM); Standardized Rhinoconjunctivitis Quality of Life Questionnaire ≥ 12 years; 22-item Sino-Nasal Outcome Test; Work Productivity and Activity Impairment Questionnaire for Asthma; and Physical Activity Limitation Questionnaire. A more detailed listing of assessments and the timing when they were collected are shown in Supplementary Material Table S1. During the COVID-19 public health emergency, study visits may have been conducted remotely via phone contact, virtual visits, or telemedicine visits.

Statistical Analysis

For continuous variables, descriptive statistics included the number of patients reflected in the calculation (n), mean, median, 25th percentile, 75th percentile, standard deviation (SD), minimum, and maximum. For categorical data, frequencies and percentages were provided.

RESULTS

Demographic Characteristics

Data from 205 patients were extracted for analysis. Of these patients, 84.9% were enrolled in the USA, 5.4% in Puerto Rico, 6.3% in Denmark, and 3.4% in Sweden. Enrolled patients were between 12 and 85 years of age (Table 1). Most patients were adults (95.1%), and 65.4% were female. Overall, the mean body mass index (BMI) was 30.7 (SD: 8.0) kg/m^2, and the proportion of patients with a BMI ≥ 30 kg/m^2 was 42.4% in adults and 0.5% in adolescent patients; 29.8% of adult and 1.0% of adolescent patients had a BMI between 25 and < 30 kg/m^2; and 17.6% of adult and 3.4% of adolescent patients had a BMI < 25 kg/m^2. Of the patients, 74.1% were white (including 12.7% individuals reporting

Table 1 Baseline demographic characteristics

Demographic characteristics	Total (N = 205)
Age, mean (SD), years	50.1 (17.4)
Age, range, years	12–85
Age groups, *n* (%)	
≥ 12 to < 18 years	10 (4.9)
≥ 18 to < 65 years	150 (73.1)
≥ 65 years	45 (22.0)
Gender, *n* (%)	
Female	134 (65.4)
Male	71 (34.6)
BMI, mean (SD), kg/m^2	30.7 (8.0)
BMI, range, kg/m^2	13.9–63.3
BMI groups, *n* (%)	
< 25 kg/m^2	43 (21.0)
≥ 25 to < 30 kg/m^2	63 (30.7)
≥ 30 kg/m^2	88 (42.9)
Missing	11 (5.4)
Race, *n* (%)	
White	152 (74.1)
Black or African-American	27 (13.2)
Asian	2 (1.0)
Multiple[a]	2 (1.0)
Other[b]	6 (2.9)
Not reported[c]	15 (7.3)
Missing	1 (0.5)
Ethnicity, *n* (%)	
Not Hispanic or Latino	162 (79.0)
Hispanic or Latino	35 (17.1)
Not reported[d]	6 (2.9)
Unknown[e]	2 (1.0)
Missing	0

BMI body mass index, *SD* standard deviation

[a]Defined as patients who have reported multiple races

[b]Patients reporting race as not white, Black or African American, or Asian

[c]Proactively no race reporting

[d]Proactively no ethnicity reporting

[e]As reported on questionnaire (entry value)

being of Hispanic or Latin origin and 47.8% female), 13.2% were Black or African American (9.3% female patients), 1.0% were Asian, and 2.9% reported "Other".

Patient Characteristics

Of the 205 patients included in this analysis, 86.8% had moderate-to-severe asthma (GINA steps 3–5) and 6.3% were categorized as mild (GINA steps 1 or 2) (Table 2). Baseline clinical characteristics in patients initiating dupilumab for asthma in clinical practice are shown in Table 2. Overall, 35.6% of patients were aged < 18 years at the onset of their asthma. Median age of onset for the overall population at asthma diagnosis was 30 years (Q1–Q3: 8.0–49.0), and the mean time since the first asthma diagnosis was 20.9 years (SD: 17.8). Additionally, 24.4% were current or former smokers (Table 2).

Beyond high-dose ICS, 64.9% of patients reported the use of ICS plus long-acting β_2-agonists as asthma controller medications in the 3 months before screening, 41.5% of patients reported the use of leukotriene receptor antagonists, and 23.9% of patients reported the use of long-acting muscarinic antagonists (Table 3). Concomitant SCS use within the 3 months prior to screening was reported by 4.9% of patients (Table 3). 12.7% of patients reported ongoing SCS use at screening, with the most common conditions prompting SCS prescription being asthma history and asthma adverse events.

Ongoing coexisting type 2 inflammatory conditions were also analyzed. Of 195 patients, 85.6% reported more than 1 coexisting condition (Table 4). The most common were allergic rhinitis (84.6%), chronic rhinosinusitis (41.5%), allergic conjunctivitis (30.3%), atopic dermatitis (28.2%), and nasal polyps (27.7%).

Disease Characteristics

At baseline, patients had a mean pre-bronchodilator FEV_1 of 2.3 (SD: 1.1) L, mean pre-bronchodilator percent predicted (pp) FEV_1 of 70.3 (SD: 20.3) %, mean forced vital capacity (FVC) of 3.1 (SD: 1.1) L, mean FEV_1/FVC ratio of 0.75 (SD: 0.4), and a mean peak expiratory flow of 356.9 (SD: 169.8) L/min (Table 5). Of the 205 patients enrolled in RAPID, 193 (94.1%) and 192 (93.7%) completed the ACQ-6 and the Asthma Quality of Life Questionnaire (AQLQ) questionnaires, respectively. The mean ACQ-6 score was 2.4 (SD: 1.2), and the mean AQLQ global score was 4.1 (SD: 1.3) (Table 5).

Baseline blood eosinophil counts were measured in 64 patients. The mean (SD) blood eosinophil count was 492.7 (443.5) cells/μL with a median (Q1–Q3) of 305.0 (200.0–695.0) cells/μL (Table 4). By category, 15.6% of patients had blood eosinophil counts below 150 cells/μL,

Table 2 Baseline clinical characteristics in patients initiating dupilumab for asthma

Clinical characteristics	Total ($N = 205$)
GINA severity score, *n* (%)	
1	5 (2.4)
2	8 (3.9)
3	29 (14.1)
4	49 (23.9)
5	100 (48.8)
Missing	14 (6.8)
Time since first asthma diagnosis, mean (SD), years	20.9 (17.8)
Age at diagnosis of asthma, median (Q1–Q3), years	30.0 (8.0–49.0)
Age at onset of asthma, *n* (%)	
< 18 years	73 (35.6)
≥ 18 to ≤ 40 years	54 (26.3)
> 40 years	78 (38.0)
Smoking history, *n* (%)	
Current	9 (4.4)
Former	41 (20.0)
Never	151 (73.7)
Unknown	4 (2.0)

GINA Global Initiative for Asthma, *Q1* first quartile, *Q3* third quartile, *SD* standard deviation

Table 3 Baseline treatment history at time of enrollment

Medications used	Total ($N = 205$)
Asthma controller medications before study enrollment, *n* (%)[b]	
SABA	1 (0.5)
ICS + LABA	133 (64.9)
ICS + LABA + LAMA	32 (15.6)
LTRA	85 (41.5)
LAMA	49 (23.9)
Biologics	19 (9.33)
ICS	24 (11.7)
LABA + LAMA/SABA + SAMA/LABA/other	17 (8.5)
Uncoded	2 (1.0)
Asthma controller medications that were ongoing at screening, *n* (%)	
SABA	1 (0.5)
ICS + LABA	112 (54.7)
ICS + LABA + LAMA	23 (11.3)
LTRA	82 (40.0)
LAMA	43 (21.0)
Biologics	6 (2.9)
ICS	17 (8.3)
LABA + LAMA/SABA + SAMA/LABA/other	16 (8.00)
Uncoded	1 (0.5)
Prior SCS medication use, *n* (%)	
Prednisone	9 (4.4)
Prednisolone	1 (0.5)
Ongoing SCS medication use at screening, *n* (%)	
Prednisone	25 (12.2)
Dexamethasone	1 (0.5)
Condition prompting SCS prescription, *n* (%)	
Asthma history	27 (13.2)
Asthma adverse event	14 (6.8)
Non-asthma adverse event	9 (4.4)
Medical history	5 (2.4)
Type 2 inflammatory comorbidity history (except asthma)	1 (0.5)

Medications at baseline are defined as any medication started before study and continued at or after study start

ICS inhaled corticosteroid(s), *LABA* long-acting β_2-agonist(s), *LAMA* long-acting muscarinic antagonist(s), *LTRA* leukotriene receptor antagonist(s), *SABA* short-acting β_2-agonist(s), *SAMA* short-acting muscarinic antagonist(s), *SCS* systemic corticosteroid(s)

Table 4 Baseline type 2 inflammatory parameters in patients initiating dupilumab for asthma

Type 2 inflammatory parameters	Total (*N* = 205)
Blood eosinophil count, cells/μL	*n1* = 64
Mean (SD)	492.7 (443.5)
Median (Q1–Q3)	305.0 (200.0–695.0)
Blood eosinophil count category, *n/n1* (%)	
< 150 cells/μL	10 (15.6)
≥ 150 to < 300 cells/μL	15 (23.4)
≥ 300 to < 500 cells/μL	17 (26.6)
≥ 500 cells/μL	22 (34.4)
FeNO, ppb	*n2* = 61
Mean (SD)	42.2 (34.8)
Median (Q1–Q3)	34.0 (16.0–56.0)
Range (ppb)	4.0–186.0
FeNO category, *n/n2* (%)	
< 25 ppb	22 (36.1)
≥ 25 to < 50 ppb	19 (31.1)
≥ 50 ppb	20 (32.8)
Ongoing coexisting type 2 inflammatory conditions, *n/n3* (%)	*n3* = 195
> 1 coexisting condition	167 (85.6)
Allergic rhinitis	165 (84.6)
Chronic rhinosinusitis	81 (41.5)
Allergic conjunctivitis	59 (30.3)
Atopic dermatitis	55 (28.2)
Nasal polyps	54 (27.7)
Food allergy	46 (23.6)
Chronic rhinosinusitis with nasal polyps	43 (22.1)
Hives/urticaria	31 (15.9)
NSAID- or aspirin-exacerbated respiratory disease	15 (7.7)
Eosinophilic esophagitis	6 (3.1)
Allergic bronchopulmonary aspergillosis	0

FeNO fractional exhaled nitric oxide, *NSAID* non-steroidal anti-inflammatory drug, *ppb* parts per billion, *Q1* first quartile, *Q3* third quartile, *SD* standard deviation

23.4% had blood eosinophil counts between ≥ 150 and < 300 cells/μL, 26.6% had blood eosinophil counts between ≥ 300 and < 500 cells/μL, and 34.4% had blood eosinophil counts ≥ 500 cells/μL. Baseline FeNO levels were measured in 61 patients. Mean (SD) FeNO was 42.2 (34.8) parts per billion (ppb), ranging between 4.0 and 186.0 ppb, with a median (Q1–Q3) of 34.0 (16.0–56.0) ppb (Table 4). Baseline FeNO levels were < 25 ppb in 36.1% of patients, 25 to < 50 ppb in 31.1%, and ≥ 50 ppb in 32.8% of patients.

Previous Asthma Exacerbations and Hospitalizations

Data on severe exacerbation events in the year before enrollment in RAPID were available for 152/205 (74.1%) patients with a mean (SD) of 2.2 (5.1) exacerbation events. Of the 152 patients, 78 (51.3%) reported severe exacerbation events in the year before enrollment, with mean of 4.4 (SD: 6.4) and median of 2.0 (Q1–Q3: 1.0–4.0) severe exacerbations, and the mean time since last exacerbation was 10.6 (SD: 15.7) months (Table 5). Of the 78 patients with a severe exacerbation event in the previous year, 57.7% had 1 to 2 severe exacerbations, and 42.3% experienced ≥ 3 severe exacerbations (Table 5). 9.3% of patients reported hospitalization and 18.5% reported emergency room visits in the year before study enrollment; among those, 4.4% reported both. The mean number of hospitalizations in the previous year was 0.2 (SD: 0.8).

DISCUSSION

In this real-world study, we have provided a comprehensive characterization of patients with asthma initiating treatment with dupilumab in clinical practice. These data come from the patient population participating in RAPID, the first real-world registry of dupilumab initiated in patients with asthma. Patients were between 12 and 85 years of age, predominantly female and non-smokers, and the most prevalent reported race was white. Most patients (86.8%) had moderate-to-severe asthma according to GINA classification [1]. Patients had a mean 20.9 (median: 15.5)-year history since asthma diagnosis and experienced frequent exacerbations, with a mean of 4.4 severe asthma exacerbations reported in the year before enrollment in 78 of 152 patients with available data.

The patients' mean BMI was elevated at 30.7 kg/m^2 (range: 13.9–63.3 kg/m^2). It has been shown that an increased BMI is associated with decreased FVC and FEV_1 [21]. Obesity is commonly defined as BMI ≥ 30 kg/m^2 [22] and is a common comorbidity of asthma [23, 24] that is associated with severity, worse asthma control, and poor response to therapy [23, 25, 26]. Furthermore, sleep-disordered breathing that can affect patients with obesity is also associated with difficult-to-control asthma [27, 28]. The highest proportion of adult patients enrolling in RAPID had a BMI ≥ 30 kg/m^2 and the lowest proportion had a BMI < 25 kg/m^2. In adolescent patients enrolled in the study, the opposite was observed, with the highest proportion having a BMI < 25 kg/m^2 and the lowest proportion of adolescent patients having a BMI ≥ 30 kg/m^2.

The population enrolling in the registry had impaired lung function, poor asthma control, and reduced asthma-related quality of life before initiating biologic therapy with dupilumab. These characteristics were expected in patients with moderate-to-severe asthma, the target population as per the dupilumab prescribing information [29]. Unexpectedly, 20.4% of patients (Table 2) presented with less severe asthma based on the GINA classification scores (GINA 1–3). The therapeutic decision to prescribe dupilumab to these patients may have been driven by, for example, persistent symptoms, a high number of exacerbations, or a limited response to maintenance therapy. The presence of multiple, less severe, coexisting type 2 inflammatory conditions could also explain the initiation of dupilumab in this subgroup. This hypothesis is supported by the finding that 85.6% of patients (167/195) had > 1 coexisting type 2 inflammatory condition. However, further data are needed to better understand the reasons to prescribe a biologic for the treatment of asthma in these patients.

Table 5 Baseline disease characteristics and PRO measures

Disease characteristics[a]	Total ($N = 205$)
Severe asthma exacerbations experienced during the year before screening, ($n = 152$)[b]	
Mean (SD)	2.2 (5.1)
Median (Q1–Q3)	1.0 (0.0–2.0)
Patients without severe exacerbation events in the year before screening, *n* (%)	74/152 (48.7)
Patients experiencing ≥ 1 severe exacerbation event in the year before screening, *n* (%)	78/152 (51.3)
Mean (SD) ($n = 78/152$)	4.4 (6.4)
Median (Q1–Q3) ($n = 78/152$)	2.0 (1.0–4.0)
Proportion of patients who experienced severe asthma exacerbations in the year before the study, *n* (%) ($n = 78$)	
1–2 exacerbations	45 (57.7)
≥ 3 exacerbations	33 (42.3)
Time since last severe asthma exacerbation, months ($n = 108$)	10.6 (15.7)
Pre-bronchodilator FEV_1, L ($n = 89$)	2.3 (1.1)
Pre-bronchodilator $ppFEV_1$, % ($n = 100$)	70.3 (20.3)
Post-bronchodilator FEV_1, L ($n = 44$)	2.5 (1.2)
Post-bronchodilator $ppFEV_1$, % ($n = 54$)	76.2 (18.0)
FVC, L ($n = 89$)	3.1 (1.1)
Pre-bronchodilator FEV_1/FVC ($n = 89$)	0.8 (0.4)
PEF, L/min ($n = 68$)	356.9 (169.8)
PRO measures	
ACQ-6 score ($n = 193$)	2.4 (1.2)
AQLQ global score ($n = 192$)	4.1 (1.3)

ACQ-6 6-item Asthma Control Questionnaire, *AQLQ* Asthma Quality of Life Questionnaire, *FEV_1* forced expiratory volume in 1 second, *FVC* forced vital capacity, *PEF* peak expiratory flow, *$ppFEV_1$* percent predicted FEV_1, *PRO* patient-reported outcome, *Q1* first quartile, *Q3* third quartile, *SD* standard deviation

[a]All data are shown as mean (SD) unless stated otherwise. [b]Missing data on severe exacerbation events in the year before screening in 53/205 (25.9%) patients

With the emergence of personalized medicine over the past decade, the use of biomarkers such as blood eosinophil counts, FeNO levels, or IgE has become a cornerstone in the diagnosis of asthma and in determining optimal treatment [30]. Unexpectedly, biomarker levels were recorded in only approximately one-third of patients enrolled in the RAPID registry, despite being prescribed a biologic. It is worth noting that the study protocol did not include a regular schedule to test blood eosinophil counts and IgE but included guidance to test these as per local standard of care. Taken together, this might suggest that biomarker measurements are not yet widely applied and are often underused in clinical settings. This could be, among other reasons, due to biomarker tests not being easily accessible or a lack of awareness of their utility.

The patients with available biomarker measurements were found to mostly have elevated

blood eosinophil counts (median 305.0 cells/μL), with one-third of patients having blood eosinophil counts ≥ 500 cells/μL, and also elevated FeNO levels (Table 4), which is consistent with observations in patient populations with moderate-to-severe asthma. This is also indicative of a type 2 inflammatory phenotype in the enrolled patients, which is representative of the patient populations enrolled in previous dupilumab asthma trials [12–15]. In terms of asthma severity measured by the number of severe exacerbations in the prior year, this initial patient cohort from RAPID reported approximately twice the number of severe exacerbations (mean 4.4 (Table 5) vs. 2.09) reported in QUEST (13). However, the RAPID cohort reported better baseline lung function than the patients in QUEST.

Smoking is known to negatively impact clinical and therapeutic outcomes of asthma treatments and results in poorer asthma control [31–34]. However, to avoid potential confusion with chronic obstructive pulmonary disease, smoking is also a main exclusion criterion for patient enrollment in asthma clinical trials, despite approximately 50% of adult patients with asthma reporting that they are currently smoking or have smoked in the past [33]. Incidentally, the number of patients with asthma recorded as smokers in previous real-world studies of biologic therapy for asthma has been reported to range between 0 and 41% in a recent systematic review [35]. At the time of this analysis, 24.4% of patients in RAPID were current or former smokers. The inclusion of this patient population bears importance and may give new insights into asthma control and asthma management in this subpopulation.

Future publications will report on the efficacy and safety of dupilumab in the real-world RAPID registry. Compared to the dupilumab phase 3 clinical trials [13, 14], RAPID allowed the enrollment of patients who were active and former smokers. Additionally, RAPID enrolled patients with a similar burden of severe exacerbations and better lung function, but worse inflammatory biomarkers and more type 2 inflammatory conditions. The presence of type 2 inflammation and/or comorbidities can increase the burden of asthma and worsen disease outcomes [36] but may also predict response to biologics [37]. Therefore, it is important to evaluate their impact in a real-world setting to confirm their relevance when deciding on treatment options.

We acknowledge that the study has some limitations inherent to its design as a registry study, which provides a much less strict treatment environment than controlled clinical trials. It has been shown that race and ethnicity are factors in the prevalence and severity of asthma. Therefore, when interpreting these results, it should be considered that, in this initial analysis of 205 patients enrolled in the study, the patient population lacked diversity: a majority of patients were white and from the USA. However, the study is ongoing (with an estimated completion date in 2025 across 8 countries worldwide and an enrollment target of 700 patients), with the goal of ensuring patient diversity and outcomes that are representative of different patient populations. Another limitation is the reporting of biologics as a prior controller medication in this study, pointing to the variation among physicians regarding the definition of a controller medicine.

CONCLUSION

RAPID is the first global registry to characterize patients initiating treatment with dupilumab in a real-world setting. In this large real-world registry of patients with asthma receiving dupilumab, participants at baseline had poor asthma control, reduced lung function, high exacerbation rates, and elevated biomarkers of type 2 inflammation in asthma, such as high eosinophils and FeNO, delineating a population with a high burden of disease despite current standard-of-care treatment before starting with dupilumab. High incidences of obesity and smoking (currently or in the past) are characteristics that worsen asthma and usually result in exclusion from clinical trials; both could account, at least partially, for this high disease burden. Overall, the data presented here provide accurate real-world evidence from patients currently enrolled in the registry, and expand on observations from previous dupilumab asthma clinical trials [12–15].

These data also provide valuable insights into the real-world application of dupilumab treatment in patients with asthma.

Medical Writing/Editorial Assistance. Medical writing/editorial assistance was provided by Bruno Manso, PhD, and Orthis Saha, PhD, of Excerpta Medica, and was funded by Sanofi and Regeneron Pharmaceuticals Inc., according to the Good Publication Practice guidelines.

Author Contributions. Lucía de Prado Gómez, Paul J. Rowe, Juby A. Jacob-Nara, Xavier Soler, Changming Xia, Yi Zhang, Amr Radwan, and Yamo Deniz contributed to the conception and design of the study. Njira L. Lugogo, Yasuhiro Gon, Andréanne Côté, Ole Hilberg, and Anju T. Peters acquired data. Changming Xia performed statistical analyses. All authors participated in protocol design, interpretation of the data, provided critical feedback and final approval for submission, and took responsibility for the accuracy, completeness, and protocol adherence of data and analyses.

Funding. The research, journal rapid service fee, and the open access fee were sponsored by Sanofi and Regeneron Pharmaceuticals Inc.

Data Availability. Qualified researchers may request access to study documents (including the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan) that support the methods and findings reported in this manuscript. Individual anonymized participant data will be considered for sharing once the indication has been approved by a regulatory body, if there is legal authority to share the data and there is not a reasonable likelihood of participant re-identification. Submit requests to https://vivli.org.

Declarations

Conflict of Interest. Njira L. Lugogo reports consulting fees from Amgen, AstraZeneca, Avillion, Genentech, GSK, Novartis, Regeneron Pharmaceuticals Inc., Sanofi, and Teva; honoraria for non-speakers bureau presentations from AstraZeneca and GSK; and travel support from AstraZeneca. Her institution received research support from Amgen, AstraZeneca, Avillion, Evidera, Gossamer Bio, Genentech, GSK, Novartis, Regeneron Pharmaceuticals Inc., Sanofi, and Teva. She is an honorary faculty member of the Observational and Pragmatic Research Institute (OPRI) but does not receive compensation for this role. Xavier Soler, Changming Xia, Amr Radwan, and Yamo Deniz are Regeneron Pharmaceuticals Inc. employees and shareholders. Yasuhiro Gon reports research, speaker fees, and consultancy fees from AstraZeneca, GSK, Kyorin Pharmaceutical, Novartis, and Sanofi. Andréanne Coté is a member of the advisory boards for AstraZeneca, GSK, Sanofi, and Valeo; has received speaker fees from AstraZeneca, GSK, and Sanofi; and has received research support from GSK and AstraZeneca. Ole Hilberg is member of Sanofi advisory boards. Yi Zhang is a former Regeneron Pharmaceuticals Inc. employee and shareholder. Lucía de Prado Gómez, Paul J. Rowe, and Juby A. Jacob-Nara are Sanofi employees and may hold stock and/or stock options in the company. Anju T. Peters has received research and consulting support from AstraZeneca, GSK, Merck, Optinose, Regeneron Pharmaceuticals Inc., and Sanofi.

Ethical Approval. RAPID is being conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonisation Good Clinical Practice guideline, and applicable regulatory requirements. The RAPID protocol was reviewed and approved by the respective institutional review boards before patient recruitment. All patients provided written informed consent. For patients under the age of 18 years, both parental/legal guardian consent and patient assent were required.

REFERENCES

1. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. 2022. Available at: https://ginasthma.org/wp-content/uploads/2022/07/GINA-Main-Report-2022-FINAL-22-07-01-WMS.pdf. Accessed July 27, 2023.

2. World Health Organization. Asthma. 2023. Available at: https://www.who.int/news-room/fact-sheets/detail/asthma. Accessed July 27, 2023.

3. US Centers for Disease Control. Uncontrolled Asthma Among Adults. 2019. Available at: https://www.cdc.gov/asthma/asthma_stats/uncontrolled-asthma-adults-2019.htm. Accessed July 27, 2023.

4. Canonica GW, Blasi F, Crimi N, et al. Defining type 2 asthma and patients eligible for dupilumab in Italy: a biomarker-based analysis. Clin Mol Allergy. 2021;19:5.

5. Pavord ID. Asthma phenotypes. Semin Respir Crit Care Med. 2012;33:645–52.

6. Fahy JV. Type 2 inflammation in asthma–present in most, absent in many. Nat Rev Immunol. 2015;15:57–65.

7. Chodankar D. Introduction to real-world evidence studies. Perspect Clin Res. 2021;12:171–4.

8. Macdonald LE, Karow M, Stevens S, et al. Precise and in situ genetic humanization of 6 Mb of mouse immunoglobulin genes. Proc Natl Acad Sci U S A. 2014;111:5147–52.

9. Murphy AJ, Macdonald LE, Stevens S, et al. Mice with megabase humanization of their immunoglobulin genes generate antibodies as efficiently as normal mice. Proc Natl Acad Sci U S A. 2014;111:5153–8.

10. Gandhi NA, Pirozzi G, Graham NMH. Commonality of the IL-4/IL-13 pathway in atopic diseases. Expert Rev Clin Immunol. 2017;13:425–37.

11. Le Floch A, Allinne J, Nagashima K, et al. Dual blockade of IL-4 and IL-13 with dupilumab, an IL-4Rα antibody, is required to broadly inhibit type 2 inflammation. Allergy. 2020;75:1188–204.

12. Wenzel S, Castro M, Corren J, et al. Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting β2 agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial. Lancet. 2016;388:31–44.

13. Castro M, Corren J, Pavord ID, et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. N Engl J Med. 2018;378:2486–96.

14. Rabe KF, Parameswaran N, Brusselle G, et al. Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma. N Engl J Med. 2018;378:2475–85.

15. Wechsler ME, Ford LB, Maspero JF, et al. Long-term safety and efficacy of dupilumab in patients with moderate-to-severe asthma (TRAVERSE): an open-label extension study. Lancet Respir Med. 2022;10:11–25.

16. Gall R, Jain N, Soong W, et al. Dupilumab-treated patients with asthma in the real world: the RAPID global registry. Adv Ther. 2023;40:1292–8.

17. Reddel HK, Taylor DR, Bateman ED, et al. An Official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. Am J Respir Crit Care Med. 2009;180:59–99.

18. Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. Eur Respir J. 1999;14:902–7.

19. Juniper EF, Svensson K, Mörk A-C, Ståhl E. Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. Respir Med. 2005;99:553–8.

20. Juniper EF, Guyatt GH, Cox FM, Ferrie PJ, King DR. Development and validation of the Mini Asthma Quality of Life Questionnaire. Eur Respir J. 1999;14:32–8.

21. Liu J, Xu H, Cupples LA, O'Connor GT, Liu C-T. The impact of obesity on lung function measurements and respiratory disease: a Mendelian

randomization study [abstract]. Ann Hum Genet. 2023;87:174–83.

22. World Health Organization. Obesity. 2021. Available at: https://www.who.int/news-room/facts-in-pictures/detail/6-facts-on-obesity. Accessed July 27, 2023.

23. Garcia-Rio F, Alvarez-Puebla MJ, Esteban-Gorgojo I, Barranco P, Olaguibel JM. Obesity and asthma: key clinical questions. J Investig Allergol Clin Immunol. 2019;29:262–71.

24. Miethe S, Karsonova A, Karaulov A, Renz H. Obesity and asthma. J Allergy Clin Immunol. 2020;146:685–93.

25. Han X, He X, Hao G, Cao L, Qi Y, Han K. The association of asthma duration with body mass index and weight-adjusted-waist index in a nationwide study of the U.S. adults. Eur J Med Res. 2023;28:122.

26. Guerrero SC, Panettieri RA Jr, Rastogi D. Mechanistic links between obesity and airway pathobiology inform therapies for obesity-related asthma. Paediatr Drugs. 2023;25:283–99.

27. Alterki A, Abu-Farha M, Al Shawaf E, Al-Mulla F, Abubaker J. Investigating the relationship between obstructive sleep apnoea, inflammation and cardio-metabolic diseases. Int J Mol Sci. 2023;24:6807.

28. Wang D, Zhou Y, Chen R, et al. The relationship between obstructive sleep apnea and asthma severity and vice versa: a systematic review and meta-analysis. Eur J Med Res. 2023;28:139.

29. DUPIXENT® (dupilumab). Highlights of Prescribing Information. US Food and Drug Administration. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761055s044lbl.pdf. Accessed 27 July 2023.

30. Guida G, Bagnasco D, Carriero V, et al. Critical evaluation of asthma biomarkers in clinical practice. Front Med (Lausanne). 2022;9:969243.

31. Tommola M, Ilmarinen P, Tuomisto LE, et al. The effect of smoking on lung function: a clinical study of adult-onset asthma. Eur Respir J. 2016;48:1298–306.

32. Jaakkola JJK, Hernberg S, Lajunen TK, Sripaijboonkij P, Malmberg LP, Jaakkola MS. Smoking and lung function among adults with newly onset asthma. BMJ Open Respir Res. 2019;6:e000377.

33. Thomson NC, Polosa R, Sin DD. Cigarette smoking and asthma. J Allergy Clin Immunol Pract. 2022;10:2783–97.

34. Takala J, Vähätalo I, Tuomisto LE, Niemelä O, Ilmarinen P, Kankaanranta H. Documentation of smoking in scheduled asthma contacts in primary health care: a 12-year follow-up study. NPJ Prim Care Respir Med. 2022;32:44.

35. Charles D, Shanley J, Temple SN, Rattu A, Khaleva E, Roberts G. Real-world efficacy of treatment with benralizumab, dupilumab, mepolizumab and reslizumab for severe asthma: a systematic review and meta-analysis. Clin Exp Allergy. 2022;52:616–27.

36. Scelo G, Torres-Duque CA, Maspero J, et al. Analysis of comorbidities and multimorbidity in adult patients in the International Severe Asthma Registry. Ann Allergy Asthma Immunol. 2024;132:42–53.

37. Wechsler ME, Scelo G, Larenas-Linnemann DES, et al. Association between T2-related comorbidities and effectiveness of biologics in severe asthma. Am J Respir Crit Care Med. 2024;209:262–72.