Baseline Demographics and Severity and Burden of Atopic Dermatitis in Adult Patients Initiating Dupilumab Treatment in a Real-World Registry (PROSE)

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ABSTRACT

Introduction: Dupilumab was initially approved in 2017 as the first biologic therapy for atopic dermatitis (AD). We characterized adults with AD initiating dupilumab in a real-world setting in the USA/Canada.

Methods: PROSE is an ongoing, longitudinal, prospective, observational, multicenter registry of patients with AD initiating dupilumab per country-specific prescribing information. We report baseline data (day of first dupilumab injection) for patients enrolled from April 2018 through July 2019.

Results: Among 315 patients (mean age 42.5 years, 55.2% female), the median AD duration was 17.0 years; 65.4% reported a history of type 2 inflammatory comorbidities (e.g., allergic rhinitis, asthma), and 93.3% reported treatment(s) for AD in the previous year, including topical corticosteroids (90.8%), systemic corticosteroids (36.2%), and nonsteroidal systemic therapies (14.0%). In total, 89.2% had an Overall Disease Severity score of 3 (moderate) or 4 (severe). Other mean disease severity scores included the following: Eczema Area and Severity Index 16.9 (range 0–72), body surface area affected 26.8%, Patient-Oriented Eczema

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Measure 18.5 (range 0–28), Dermatology Life Quality Index 12.7 (range 0–30), and pruritus Numerical Rating Scale score 6.9 (range 0–10). *Conclusion*: Patients initiating dupilumab have longstanding moderate-to-severe AD with significant disease burden and frequent type 2 comorbidities.
ClinicalTrials.gov Identifier: NCT03428646.

Key Points

Why carry out this study?

Dupilumab was initially approved in 2017 as the first biologic therapy for atopic dermatitis (AD).

Patients with AD enrolled in dupilumab clinical trials had considerable disease burden, and this is also true for most patients receiving dupilumab treatment by prescription in the real world.

We analyzed adults in the PROSE registry study (an ongoing, longitudinal, prospective, observational, multicenter registry of US and Canadian patients with AD initiating dupilumab in a real-world setting) with respect to sociodemographics, history of AD, and other type 2 inflammatory comorbidities, AD treatment history, and disease severity measured by physician assessments and patient-reported outcomes.

What was learned from the study?

Real-world patients who initiated dupilumab had variable AD signs, symptoms, quality of life impact, and past/current treatments.

Physician assessments alone appeared to underestimate disease burden, highlighting the importance of patient-reported outcomes when selecting appropriate treatments for moderate-to-severe disease.

DIGITAL FEATURES

This article is published with digital features, including a video abstract, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.19535917.

INTRODUCTION

Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by pruritus, eczematous lesions, and upregulation of type 2 immune responses [1–3]. AD was traditionally thought to start in childhood and improve with age [4, 5]. However, data increasingly suggest that AD often continues into, or can even start during, adulthood [1, 4–6]. Recent cross-sectional evidence shows a prevalence of AD of 7.3% (16.5 million cases) among adults in the USA, of which 6.6 million (40%) are moderate to severe in severity [7]. AD can have a profound impact on quality of life (QoL) and has been associated with increased risk of depression and anxiety [7–9]. Patients with AD are also at increased risk of other inflammatory diseases driven by type 2 cytokines, e.g., asthma and allergic rhinitis [1, 10].

Dupilumab (Dupixent, Regeneron Pharmaceuticals, Inc., NY)—a fully human *VelocImmune*-derived [11, 12] monoclonal antibody—blocks the shared receptor alpha component for interleukins 4 and 13, thus inhibiting signaling of both cytokines. Dupilumab clinical trials have shown that these cytokines are key drivers of type 2 inflammation, which play a major role in AD [13–17], asthma [18], chronic rhinosinusitis with nasal polyposis [19, 20], and eosinophilic esophagitis [21]. In the USA and Canada, dupilumab is approved for the treatment of patients aged ≥ 6 years with moderate-to-severe AD not adequately controlled by topical prescription medications (or when these are not advisable) [22, 23]. Dupilumab is also indicated as add-on maintenance treatment for patients aged ≥ 6 years (USA) or ≥ 12 years (Canada) with moderate-to-severe asthma with

eosinophilic phenotype, oral corticosteroid-dependent asthma, and adults with inadequately controlled chronic rhinosinusitis with nasal polyposis [22, 23].

There is a lack of data on patients receiving dupilumab for AD in a real-world setting. Thus, the PROSE registry will study patients, treatment practices, and dupilumab effectiveness and safety in US and Canadian patients with AD who initiated dupilumab in a real-world setting. We analyzed adults in PROSE with respect to sociodemographics, history of AD and other type 2 inflammatory comorbidities, AD treatment history, and disease severity measured by physician assessments and patient-reported outcomes (PROs).

METHODS

Study Design

The PROSE registry (ClinicalTrials.gov Identifier NCT03428646) is an ongoing, longitudinal, prospective, observational study of adolescents and adults with physician-diagnosed AD who initiated dupilumab, prescribed according to country-specific prescribing information in the USA and Canada. AD was diagnosed according to physicians' clinical judgment in routine practice, as the study protocol did not mandate standardized diagnostic criteria. Consecutive patients with AD at each study site who receive an initial prescription for dupilumab are invited to participate. This interim analysis includes data from adults with a first-ever prescription of dupilumab for AD from 6 April 2018 through 28 July 2019. Appropriately constituted institutional review boards approved the study (Supplementary Table 1), which was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and is consistent with applicable regulatory requirements.

Patients

For this interim analysis, eligible patients were aged ≥ 18 years, initiated dupilumab as standard of care for AD according to country-specific prescribing information [22, 23], were willing and able to comply with study-related activities and understand and complete study-related questionnaires, and provided informed consent. Exclusion criteria included contraindication for dupilumab, any condition that could interfere with the patient's ability to participate, and prior use of dupilumab within 6 months.

Assessments

Baseline assessments were performed on the day of initial dupilumab administration. Baseline characteristics included sociodemographics, specialty of the prescriber, AD history, history of certain type 2 inflammatory comorbidities, AD treatment history, and AD characteristics.

Physician-rated AD assessments included Eczema Area and Severity Index (EASI; scale 0–72), Overall Disease Severity (ODS) score, and body surface area (BSA) affected by AD (%). For the ODS, the physician gave a rating of 0 (no), 1 (minimal), 2 (mild), 3 (moderate), or 4 (severe disease) to the question: "Taking into account all important aspects characterizing the severity of AD, how would you grade your patient's AD at this time?".

The following PROs were collected: Patient-Oriented Eczema Measure (POEM) (scale 0–28), Numerical Rating Scale (NRS) measures of skin symptoms and sleep (scale 0–10), and Dermatology Life Quality Index (DLQI) (scale 0–30) (all with higher scores indicating more severe disease/symptoms); Patient Global Assessment of Atopic Dermatitis (PGAD) and Patient's overall Assessment of Health State (PAHS) (both scale 1–5, with higher scores indicating less severe disease); Health Care Resource Utilization Questionnaire (HCRUQ; patients were asked "Over the past 3 months, have you been hospitalized, or visited the emergency room or an urgent care center because of your eczema? If yes, what was the reason?"; the number of hospitalization days and the number of urgent care or emergency room visits were also recorded); and Work Productivity and Activity Impairment Questionnaire for Atopic

Dermatitis (WPAI-AD; a six-item, validated questionnaire to measure impairments in work and activities over the past 7 days; outcomes are expressed as percentages, with higher numbers indicating greater impairment/less productivity).

Statistical Analysis

An interim analysis dataset composed of all adults who were eligible and consented to participate in the study from 6 April 2018 through 28 July 2019 was used to analyze baseline demographics, disease, and treatment history. For continuous variables, descriptive statistics included means and standard deviations (SDs) or medians with interquartile ranges (IQRs); for categorical or ordinal data, frequencies and percentages were used.

RESULTS

Among 399 patients who received a dupilumab prescription and agreed to participate, 315 (78.9%) initiated treatment with dupilumab and were included in this analysis (280 in the USA and 35 in Canada). The main reasons for exclusion were failure to initiate dupilumab within the protocol-defined 84 days following a prescription (55 patients), consent withdrawn (8 patients), and inclusion criteria not met or exclusion criteria met (6 patients). The median (IQR) time from prescription to treatment initiation was 26 (11–46) days. The delay was mainly due to the need to obtain approval for the prescription from their insurance company and schedule an appointment for administering the injection.

Baseline Sociodemographic Characteristics

The mean (SD) age was 42.5 (17.0) years, and 55.2% were female (Table 1). Most patients had private health insurance or belonged to a health maintenance organization (66.7%); 57.8% had at least a college education; and 60.0% were employed/self-employed (Table 1). Most

Table 1 Baseline sociodemographic characteristics

	PROSE cohort ($n = 315$)
Age, mean (SD), years	42.5 (17.0)
Age group, n (%)	
18 to < 40 years	148 (47.0)
40 to < 65 years	133 (42.2)
65 to < 75 years	27 (8.6)
≥ 75 years	7 (2.2)
Female, n (%)	174 (55.2)
Race, n (%)	
White	187 (59.4)
Black or African American	56 (17.8)
Asian	51 (16.2)
Other	7 (2.2)
Not reported	14 (4.4)
Body mass index, mean (SD), kg/m^2	28.2 (7.2) ($n = 285$)
Body mass index group, n (%)	
15 to < 25 kg/m^2	104 (33.0)
25 to < 30 kg/m^2	97 (30.8)
≥ 30 kg/m^2	84 (26.7)
Missing	30 (9.5)
Insurance information, n (%)	
Private health insurance or health maintenance organization	210 (66.7)
Medicaid	28 (8.9)
Medicare	26 (8.3)
Other	9 (2.9)
None	6 (1.9)
Missing	36 (11.4)
Highest education level, n (%)	
≤ Secondary school	58 (18.4)
University	148 (47.0)
Master's/Doctor of Philosophy/doctorate	34 (10.8)

Table 1 continued

	PROSE cohort (*n* = 315)
Other	8 (2.5)
Unknown/not reported	67 (21.3)
Employment status, *n* (%)	
Employed/self-employed	189 (60.0)
Retired	33 (10.5)
Student	24 (7.6)
Homemaker/out of work	19 (6.0)
Unable to work	16 (5.1)
Unknown/not reported	34 (10.8)
Physician information, *n* (%)	
Dermatologist	224 (71.1)
Allergist	56 (17.8)
Dermatologist/allergist	24 (7.6)
Other/none/not collected	11 (3.5)

SD standard deviation

prescribers (96.5%) were dermatologists and/or allergists (Table 1).

AD History

The median (IQR) age at AD diagnosis was 16.0 (3.0, 44.0) years, and the median (IQR) duration of AD was 17.0 (4.0, 30.0) years (Table 2). Overall, 34.9% of patients had a family history of AD.

History of Type 2 Inflammatory Comorbidities

The majority of patients (65.4%) reported a history of one or more type 2 inflammatory comorbidities, most commonly allergic rhinitis (34.9%) and asthma (29.2%); and 38.7% had ≥ 2 type 2 inflammatory comorbidities (Table 2).

Table 2 AD history

	PROSE cohort (*n* = 315)
Age at AD diagnosis, median (IQR), years	16.0 (3.0–44.0)
Duration of AD, median (IQR), years	17.0 (4.0–30.0)
Family history of AD, *n* (%)	110 (34.9)
Relationship of family member who had AD, *n* (%)	
Mother	40 (12.7)
Father	27 (8.6)
Sibling	41 (13.0)
Grandparent	13 (4.1)
Other	32 (10.2)
Any type 2 inflammatory comorbidities (except AD, ever), *n* (%)	206 (65.4)
Allergic rhinitis	110 (34.9)
Asthma	92 (29.2)
Food allergies	68 (21.6)
Allergic conjunctivitis	66 (21.0)
Other allergies	61 (19.4)
Chronic urticaria	20 (6.3)
Chronic rhinosinusitis	8 (2.5)
Nasal polyps	4 (1.3)
NSAID hypersensitivity	4 (1.3)
Atopic keratoconjunctivitis	2 (0.6)
Other atopic/allergic conditions	8 (2.5)
Number of type 2 inflammatory comorbidities (ever), *n* (%)	
1	84 (26.7)
2	52 (16.5)
3	38 (12.1)
4	21 (6.7)
5	9 (2.9)
6	2 (0.6)

Table 2 continued

	PROSE cohort (*n* = 315)
0 or missing	109 (34.6)

AD atopic dermatitis, *IQR* interquartile range, *NSAIDs* nonsteroidal anti-inflammatories

AD Treatment History

All patients reported ever receiving prior AD treatment(s), with 93.3% reporting this during the past year (Table 3). Most patients (92.7%) had ever received topical corticosteroids, and 38.4% had received topical calcineurin inhibitors (Table 3). Overall, 49.5% of patients had ever received systemic AD treatment(s): 41.0% systemic corticosteroids and 16.8% nonsteroidal systemic therapies (e.g., methotrexate, cyclosporine) (Table 3). Phototherapy was reported by 10.2% of patients (Table 3). Treatments during the previous 12 months, along with treatment durations, are detailed in Table 3.

A total of 41.9% of patients were receiving AD medication at baseline: 39.0% topical and 6.0% systemic (Table 3).

Baseline Disease Characteristics and Burden

The most common type 2 inflammatory comorbidities that were active (i.e., symptomatic and/or requiring treatment) at baseline were allergic rhinitis (22.5%), asthma (15.2%), allergic conjunctivitis (9.8%), and food allergies (9.5%) (Table 4). Overall, the population enrolled in PROSE had moderate-to-severe AD, as assessed by physicians and PROs. The mean

Table 3 AD treatment history

	PROSE cohort (*n* = 315)			
	Ever	During previous 12 months		At baseline
	n (%)	*n* (%)	Duration, mean (SD), days	*n* (%)
≥ 1 AD treatment	315 (100)	294 (93.3)	–	132 (41.9)
Topical treatment	296 (94.0)	290 (92.1)	228[b] (184)	123 (39.0)
Corticosteroids	292 (92.7)	286 (90.8)	179 (131)	106 (33.7)
Calcineurin inhibitors (tacrolimus, pimecrolimus)	121 (38.4)	113 (35.9)	95 (111)	45 (14.3)
Phosphodiesterase-4 inhibitor (crisaborole)	69 (21.9)	62 (19.7)	66 (75)	29 (9.2)
Systemic treatment	156 (49.5)	141 (44.8)	79[b] (123)	19 (6.0)
Corticosteroids	129 (41.0)	114 (36.2)	40 (69)	8 (2.5)
Non-steroidal systemic therapies	53 (16.8)	44 (14.0)	150 (139)	12 (3.8)
Methotrexate	32 (10.2)	24 (7.6)	112 (140)	5 (1.6)
Cyclosporine	27 (8.6)	22 (7.0)	161 (135)	6 (1.9)
Mycophenolate mofetil	10 (3.2)	6 (1.9)	41 (41)	1 (0.3)
Azathioprine	3 (1.0)	2 (0.6)	75 (64)	0
Phototherapy	32 (10.2)	23 (7.3)	60 (94)	1 (0.3)

Percentages are of all patients rather than those with known medication status

AD atopic dermatitis, *SD* standard deviation

[a]Totals of durations of each treatment for each patient

Table 4 Baseline disease burden

	PROSE cohort ($n = 315$)
Any type 2 inflammatory comorbidities (except AD) active at baseline, n (%)	113 (35.9)
Allergic rhinitis	71 (22.5)
Asthma	48 (15.2)
Allergic conjunctivitis	31 (9.8)
Food allergies	30 (9.5)
Chronic urticaria	11 (3.5)
Chronic rhinosinusitis	6 (1.9)
Nasal polyps	3 (1.0)
Atopic keratoconjunctivitis	1 (0.3)
Physician-assessed AD severity	
EASI total score,[a,b] mean (SD)	16.9 (13.4) ($n = 314$)
Severity of AD lesions according to EASI,[a,b] n (%)	
Clear/almost clear (score 0 or 1)	7 (2.2)
Mild AD (score 2–7)	68 (21.6)
Moderate AD (score 8–21)	152 (48.3)
Severe AD (score $\geq$ 22)	87 (27.6)
Missing	1 (0.3)
ODS,[a] n (%)	
No disease (score 0)	2 (0.6)
Minimal disease (score 1)	4 (1.3)
Mild disease (score 2)	26 (8.3)
Moderate disease (score 3)	176 (55.9)
Severe disease (score 4)	105 (33.3)
Missing	2 (0.6)
BSA affected by AD,[a] mean (SD), %	26.8 (23.7) ($n = 313$)
PROs	
POEM,[c,d] mean (SD)	18.5 (6.7) ($n = 233$)
DLQI,[c,e] mean (SD)	12.7 (7.5) ($n = 227$)
PGAD, n (%)	
Poor (score 1)	5 (1.6)
Fair (score 2)	22 (7.0)
Good (score 3)	77 (24.4)
Very good (score 4)	69 (21.9)

Table 4 continued

	PROSE cohort (n = 315)
Excellent (score 5)	53 (16.8)
Missing	89 (28.3)
PAHS, n (%)	
Poor (score 1)	8 (2.5)
Fair (score 2)	70 (22.2)
Good (score 3)	85 (27.0)
Very good (score 4)	46 (14.6)
Excellent (score 5)	4 (1.3)
Missing	102 (32.4)
NRS,[f] mean (SD)	
Pruritus	6.9 (2.3) (n = 227)
Sleep disturbance	5.4 (3.3) (n = 224)
Skin pain/soreness	5.3 (3.0) (n = 227)
Skin sensitivity	5.1 (3.2) (n = 227)
Skin feeling hot	4.6 (3.1) (n = 226)

AD atopic dermatitis, *BSA* body surface area, *DLQI* Dermatology Life Quality Index, *EASI* Eczema Area and Severity Index, *NRS* Numerical Rating Scale, *ODS* Overall Disease Severity, *PAHS* Patient's overall Assessment of Health State, *PGAD* Patient Global Assessment of Atopic Dermatitis, *POEM* Patient-Oriented Eczema Measure, *SD* standard deviation
[a]Physician assessment at the baseline visit
[b]EASI scale 0–72, with 0–1 indicating clear/almost clear; 1.1–7, mild; 7.1–21, moderate; 21.1–50, severe; and 50.1–72, very severe [24]
[c]As rated by the patient during the past 7 days
[d]POEM scale 0–28, with 0–2 indicating clear/almost clear; 0–7 or 3–7, mild; 8–16 or 8–19, moderate; 17–24, 17–28, or 20–28, severe; 25–28, very severe [25–27]
[e]DLQI scale 0–30, with 0–5 indicating mild; 6–10, moderate; 11–30, severe [26, 27]
[f]As rated by the patient as an average during the past 7 days (scale 0–10, with 0 being none and 10 being the worst)

(SD) EASI was 16.9 (13.4) (i.e., moderate) [24]; 55.9% and 33.3% of patients were suffering from moderate and severe disease, respectively, according to ODS (Table 4).

The mean (SD) POEM score was 18.5 (6.7), consistent with moderate-to-severe disease [25–27], and the mean (SD) DLQI was 12.7 (7.5) (i.e., severe effect on QoL) [26, 27] (Table 4). Mean (SD) NRS scores ranged from 6.9 (2.3) for pruritus to 4.6 (3.1) for skin feeling hot.

Four of 227 patients who completed the HCRUQ had been hospitalized for AD [mean (SD) duration: 4.8 (4.4) days] and 26 of 226 patients had visited the emergency room during the previous 3 months for reasons such as eczema flare (n = 26), unbearable itch (n = 22), skin infection (n = 10), or other AD-related reasons (n = 8). From the WPAI-AD, during the previous 7 days, the mean (SD) percent work time missed due to AD was 4.7% (16.9%) (n = 129); AD-related impairment while working was 35.6% (31.7%) (n = 208); overall work impairment due to AD was 34.3% (28.7%) (n = 126); and activity impairment due to AD was 44.1% (32.3%) (n = 220).
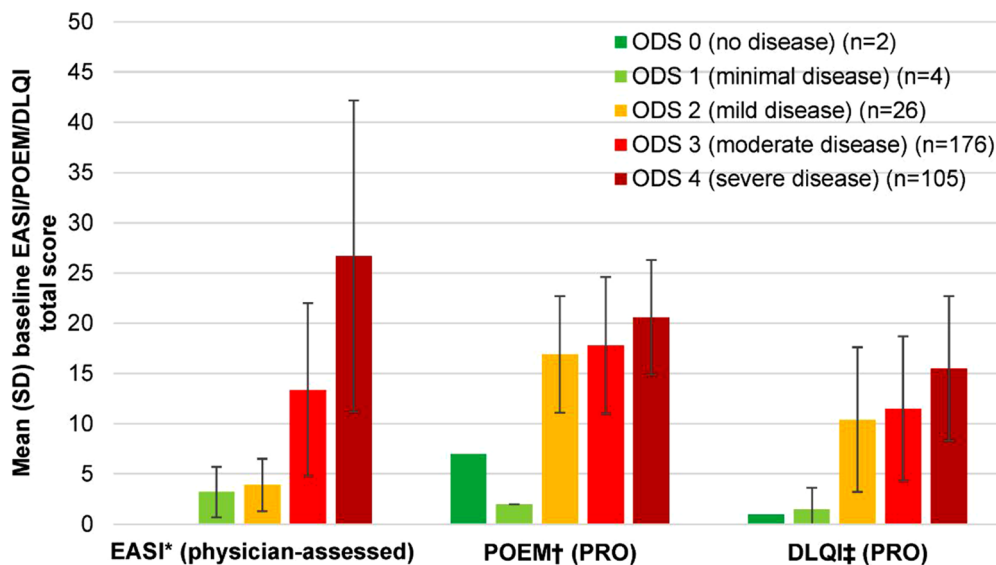
Fig. 1 Disease characteristics (EASI, POEM, DLQI) by ODS. [a]EASI scale 0–72, with 0–1 indicating clear/almost clear; 1.1–7, mild; 7.1–21, moderate; 21.1–50, severe; and 50.1–72, very severe [24]. [b]POEM scale 0–28, with 0–2 indicating clear/almost clear mild; 0–7 or 3–7, mild; 8–16 or 8–19, moderate; 17–24, 17–28, or 20–28, severe; 25–28, very severe [25–27]. [c]DLQI scale 0–30, with 0–5 indicating mild; 6–10, moderate; 11–30, severe [26, 27]. *DLQI* Dermatology Life Quality Index, *EASI* Eczema Area and Severity Index, *NA* not available, *ODS* Overall Disease Severity, *POEM* Patient-Oriented Eczema Measure, *PRO* patient-reported outcome, *SD* standard deviation

Stratification of Baseline ODS by Other Measures

Physician-assessed ODS correlated well with physician-assessed EASI, and patients with moderate disease by ODS had, on average, moderate disease by EASI, etc. (Fig. 1) [24]. However, ODS seemed to underestimate overall AD severity compared with PROs. On average, patients with physician-assessed mild or moderate ODS self-assessed their disease as moderate or severe by POEM and having a moderate-to-severe effect on their QoL by DLQI (Fig. 1) [25–27].

The correlation between baseline EASI total score and baseline pruritus NRS was low (Pearson correlation coefficient 0.227).

DISCUSSION

This analysis of the sociodemographic and AD characteristics of adults receiving a first prescription for commercially available dupilumab at selected sites in the USA and Canada shows a considerable reduction in the disease burden, with prevalent AD signs, itch, and impacted QoL despite treatment with topical and/or systemic therapies.

Patients enrolled in PROSE had a long-standing history of AD, with a median of 17.0 years since diagnosis. Two-thirds of patients had private health insurance/health maintenance organization coverage, over half had a college education, and 60.0% were employed, showing a good representation of a real-world population.

Almost two-thirds of the patients had a history of type 2 inflammatory comorbidities, and more than half of these had two or more type 2 inflammatory comorbidities. Nearly all patients had received AD treatment(s) in the previous year, with nearly half of them having received systemic treatment. Most patients had moderate or severe AD on the day of first dupilumab injection per physician assessment (EASI and ODS), but the mean patient-reported severity was generally in the severe range, as was the mean impact on QoL. Of note, we piloted the use of ODS, which is a basic questionnaire not

previously used in studies. ODS prompts the investigator to provide a physician global assessment, considering "all important aspects" that characterize AD severity. ODS was included on an exploratory basis as an alternative to the Investigator Global Assessment (IGA), which has been widely used in clinical trials to assess AD severity but is limited to acute features of lesion severity (erythema and induration/papulation) and does not take into account other important elements of AD severity, such as affected BSA, itch, sleep loss, QoL, frequency and duration of AD exacerbations, and treatment response [28]. While ODS does not specifically evaluate individual elements of disease severity (e.g., AD lesion extent and severity, patient complaints, frequency and severity of exacerbations, response to treatment, etc.), we hoped that, as a physician global assessment tool, ODS would better characterize AD severity by opening up the assessment to "all important aspects" of the patient's AD.

The baseline characteristics of adults in the current US dupilumab registry can be compared with those of patients from two published observational studies. The Japanese ADDRESS-J AD registry included adults with moderate-to-severe AD (IGA 3 or 4; scale 0–4), none of whom received dupilumab [29]. The TREatment of ATopic eczema, the Netherlands (TREAT NL) dupilumab registry included adult AD patients who started dupilumab in routine clinical care, which is available in the Netherlands after patients receive ≥ 4 months of treatment with at least one conventional systemic therapy at an adequate dose [30]. Patients in PROSE had less severe AD than those in ADDRESS-J or TREAT NL when assessed by EASI, but more severe AD than those in ADDRESS-J and less severe AD than those in TREAT NL when assessed by POEM or DLQI [29, 30]. The lower disease burden in PROSE compared with TREAT NL (in which all patients received dupilumab) may be due to the more stringent inclusion criterion in TREAT NL and/or the different health care systems in the USA and the Netherlands.

In TREAT NL [30], all patients had received systemic treatments (as per the national criteria in the Netherlands), mainly cyclosporine (89.1%), corticosteroids (61.5%), and methotrexate (46.6%) [30], while 44.8% of patients in PROSE reported systemic AD treatment in the previous year. In ADDRESS-J [29], topical treatments were widely reported as the most recent treatment before baseline (86.7%), while only 39.0% of patients in PROSE reported using a topical treatment at baseline. Another difference in the treatment patterns in the three registries is that, in PROSE and ADDRESS-J [29], very few patients had undergone phototherapy, while 75.1% of patients had undergone previous phototherapy in TREAT NL [30]. This could be due to different treatment availabilities and/or preferences in the USA, Japan, and the Netherlands, or could be related to the differences in the disease severity. Treatment differences aside, results from all three registries show that despite treatment with topical therapies, systemic therapies, and phototherapy, disease severity remained high, showing an unmet need for these patients with AD.

In PROSE, we found good agreement between physician-reported measures but poor correlations between these and PROs. Similar findings were reported in ADDRESS-J [29], showing that physicians can underestimate the impact of AD. Clearly, the different assessment tools each capture distinct features of AD, i.e., itch, lesional symptoms, QoL, etc. Hence, multiple tools are required to sufficiently characterize disease severity.

The real-world patients in PROSE are somewhat different from the patients in pivotal phase 3 dupilumab AD studies [31]. PROSE patients were more likely to be female (55% versus 37–46% across arms in SOLO 1 and 2, CHRONOS, and CAFÉ) and had lower physician-assessed AD severity (median affected BSA: 19% versus 51–59%; EASI: 14 versus 29–32) but similar PROs (median POEM: 19 versus 19–22; DLQI: 12 versus 13–15) [31]. This in part reflects the strict entry criteria for the phase 3 trials, which mandated a baseline EASI ≥ 16 (SOLO 1 and 2 [32], CHRONOS [13]) or ≥ 20 (CAFÉ [15]), and an IGA score ≥ 3. Further, there were no eligibility restrictions within PROSE concerning concomitant AD treatments at baseline or any other point, whereas the phase 3 studies required washout for topical and systemic AD

medications before initiating dupilumab [13, 15, 32].

Strengths and Limitations

In this registry of real-world patients who initiated dupilumab, the collection of comprehensive baseline data on the day of the first dupilumab administration allowed for a thorough characterization of patient sociodemographics, AD history, AD treatment history, associated type 2 comorbidities, and AD severity variables, including physician-assessed AD signs and PROs (AD symptoms and QoL measures). Post-baseline assessments in future analyses will allow for the longitudinal observation of the real-world effectiveness of dupilumab. The study will also capture safety information and health care utilization data. Furthermore, since the study did not mandate standardized diagnostic criteria, patient selection was based entirely on routine diagnostic practice by participating physicians, favoring the generalizability of these observations to "real-world" populations.

However, this study also has some limitations. Certain aspects of the study design could have formed a cohort of patients that may not be generalizable to the wider patient population. For example, the requirements for monthly PRO assessments might have garnered a more disciplined or self-motivated patient type. Further, investigative sites were not chosen to ensure representative sampling of US and Canadian patients with AD. Also, as only sites in the USA and Canada were included, the worldwide generalizability of the results is limited. Lastly, some data were missing.

CONCLUSIONS

Patients enrolled in PROSE and initiating dupilumab in the real world have longstanding moderate-to-severe AD, with significant and variable disease burden based on AD signs, symptoms, and QoL, and with frequent type 2 comorbidities. Physician assessments alone appeared to underestimate the burden of disease, highlighting the importance of PROs when selecting appropriate treatments for moderate-to-severe AD.

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Compliance with ethics guidelines. Appropriately constituted Institutional Review Boards approved the study (Supplementary Table 1), which was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and is consistent with applicable regulatory requirements. All patients provided informed consent to participate in the study.

Data Availability. The datasets generated and analyzed during the current study are not publicly available because the registry study is still ongoing and the current analysis is interim.

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