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ORIGINAL RESEARCH

Dupilumab Treatment of Atopic Dermatitis in Routine Clinical Care: Baseline Characteristics of Patients in the PROLEAD Prospective, Observational Study

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ABSTRACT

Introduction: Dupilumab is the first biologic licensed to treat patients with moderate-to-severe atopic dermatitis (AD) who require systemic therapy. PROLEAD was designed to document the real-world effectiveness and safety of dupilumab in patients with moderate-to-severe AD. The present study aims to describe the baseline characteristics of patients treated with dupilumab in Germany.

Methods: PROLEAD is a national, multicentre, prospective, non-interventional study, with a 2-year observation period. Adults with moderate-to-severe AD treated with dupilumab were included. Baseline characteristics, physician assessments, and patient-reported outcomes (PROs) were collected.

Results: The study involved 126 sites throughout Germany. Of 839 patients assessed for eligibility, 828 were included, with baseline data available for 817 patients. Mean (standard deviation, SD) age of patients was 43.4 (15.8) years, with 396 (48.5%) patients being female. Overall, 66.6% of patients received their first diagnosis of AD during childhood. In total, 423 (51.8%) patients had co-existing atopic and type 2 inflammatory diseases, including allergic conjunctivitis (36.8%) and bronchial asthma

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(22.5%). Overall, 61.4% of patients had received systemic therapy, most commonly oral corticosteroids (49.9%). Approximately half of patients (51.3%) had received UV/phototherapy prior to baseline. Treatment with moderate-potent (Class 2) or potent (Class 3) topical corticosteroids was the most common concomitant treatment at baseline. However, 50.4% of patients had not received concomitant AD treatment with dupilumab at baseline. The most reported reason for initiating dupilumab was "Topical therapy alone was not sufficient" (95.1%). Mean (SD) physician assessments: EASI: 22.9 (14.5); SCORAD: 63.3 (16.2); IGA: 3.3 (0.7). Mean (SD) PROs: DLQI: 13.9 (7.1); peak pruritus NRS: 7.4 (2.3).

Conclusions: Patients with moderate-to-severe AD present a long medical history, impaired quality of life, and high prevalence of co-existing type 2 inflammatory diseases. Dupilumab was used as a first-line systemic treatment in 38.6% of patients.

Keywords: Atopic dermatitis; Biologic; Dupliumab; Real-world evidence

Key Summary Points
Dupilumab is the first biologic licensed to treat patients with moderate-to-severe atopic dermatitis who require systemic therapy
PROLEAD was designed to document the real-world effectiveness and safety of dupilumab in this patient population
The present study describes the baseline characteristics of patients (N = 817) treated with dupilumab in Germany
Patients with moderate-to-severe AD present a long medical history, impaired quality of life, and high prevalence of co-existing type 2 inflammatory diseases
Dupilumab was used as a first-line systemic treatment in 38.6% of patients

INTRODUCTION

Moderate-to-severe atopic dermatitis (AD) is a chronic type 2 inflammatory disease characterised by impaired epidermal barrier, immunological disorders, frequent flares with intense itch, and poor quality of life (QoL) [1–3]. The reported prevalence of AD in Germany has ranged from 3.7% (n = 1.4 million) [4] to 4.2% [95% confidence interval (CI), 4.1, 4.2%; n = 3.6 million] [5], with an annual prevalence among adults aged > 20 years of 3.3%. Moreover, 31.3% of these adults present with moderate-to-severe AD, without a clear difference between the sexes [5]. A checklist developed to identify patients with moderate-to-severe AD who require systemic treatment is included in the German S2k guideline update, 'systemic treatment of atopic dermatitis' [6].

Previously, it was reported that many patients with moderate-to-severe AD experience uncontrolled disease, even after use of intensive topical treatment and/or conventional systemic regimens, such as immunosuppression [7]. This is because some immunosuppressants are only suitable for short-term use because of toxicity (ciclosporin A) or have moderate (azathioprine; off-label in Germany) or unproven (e.g., methotrexate, mycophenolate mofetil, alitretinoin; off-label in Germany) efficacy [6]. As such, disease control, including freedom from itching (often rated by patients as important), is a priority for patients with moderate-to-severe AD [8]. However, it has been reported that patients with AD are undersupplied with treatments, with approximately one-third of patients being treated by a specialist. In addition, innovative treatments, such as dupilumab, are so far rarely prescribed (0.64%) and are primarily prescribed by dermatologists (66.7%) [5].

Dupilumab (Dupixent®) [9], the first biologic licensed for adults and adolescents with moderate-to-severe AD who require systemic therapy, is also licensed in patients aged ≥ 6 years with severe AD [10] and in other type 2 inflammatory diseases [1, 11]. Dupilumab is a fully human monoclonal antibody that blocks the interleukin (IL)-4 and IL-13 signalling pathways, which are key drivers of type

2 inflammation in AD and other type 2 inflammatory diseases, such as severe asthma and chronic rhinosinusitis with nasal polyps [2, 3]. In the pivotal phase III CHRONOS study, dupilumab improved the signs and symptoms of AD compared with placebo, with favourable safety, when added to standard topical corticosteroid (TCS) treatment for 1 year in adults with moderate-to-severe AD [12]. Real-world studies have demonstrated improvements in signs, symptoms and QoL in patients of various age groups that were treated with dupilumab for moderate-to-severe AD. These included two prospective studies conducted in adolescents [13] and adults [14] and a retrospective study in elderly patients (aged $\geq$ 65 years) [15].

PROLEAD is the largest prospective, non-interventional study in Europe to investigate the effectiveness and safety of dupilumab in adult patients with moderate-to-severe AD in a real-world setting and how patients transition from prior AD treatments to dupilumab in real life. Reported here are baseline characteristics of patients in PROLEAD, reflecting the patients who are usually treated with dupilumab in Germany.

METHODS

Study Design

PROLEAD is a national, multicentre, prospective, non-interventional study in Germany, with a 2-year observation period. The primary objective is to document the real-world effectiveness of dupilumab in routine clinical practice as treatment for moderate-to-severe AD. Secondary objectives include documentation of the safety of dupilumab, patient medical history and characteristics, prior and concomitant AD treatment, and reasons for initiating dupilumab.

The transition period from prior treatments to dupilumab was assessed retrospectively, and concomitant treatments at baseline and thereafter, and measures of dupilumab effectiveness and safety, are assessed prospectively. The documentation period for inclusion of patients started on 13 April 2018 (first patient in) and ended on 30 September 2020 (last patient in). The current analysis was performed based on the data cut on 1 October 2021 and includes baseline values from all patients.

Participants

PROLEAD included patients with moderate-to-severe AD for whom the decision to start treatment was made before and independently from inclusion into this study. Included patients were those treated for the first time with dupilumab as indicated by the Summary of Product Characteristics (SmPC) [9]. All patients were $\geq$ 18 years of age and provided written informed consent. Exclusion criteria included contraindication to dupilumab (hypersensitivity to active ingredient or any of the excipients) [9], treatment with $>$ 2 injections of dupilumab within 3 weeks before inclusion, or treatment with an investigational drug within 3 months prior to study inclusion.

Assessments

Patient data are collected at baseline (treatment initiation), Month 1, Month 3, and every 3 months thereafter until the end of the total 2-year observational period or dupilumab withdrawal. Data collected at baseline included: patient demographics; current and past comorbidities and concomitant diseases; family history of atopic diseases; patient-reported lifetime history of treatment for signs and symptoms of AD; AD treatments prior to baseline; concomitant medication; current and past burden and severity of disease; reasons for discontinuing previous treatments and for initiating dupilumab; and baseline scores for physician- and patient-reported outcome measures of disease severity and burden. Patients also fulfilled the checklist criteria for systemic treatment of AD [6]: relevant sleep disturbance was defined as $>$ 6 in the respective Patient-Oriented SCORing Atopic Dermatitis (PO-SCORAD) question or patients answering the Patient Oriented Eczema Measure (POEM) question 2 with '5–6 nights' or 'every day').

Data Collection

This study involves primary data collection by treating dermatologists and their patients. Routine clinical documentation records used include medical charts, physician assessments (eczema area and severity index [EASI], SCORing atopic dermatitis [SCORAD], Investigator's global assessment [IGA], and bespoke questions concerning past exacerbations, hospital visits/stays, and recent treatments), patient-completed questionnaires (POEM, dermatology life quality index [DLQI], five-level EuroQol five-dimensional questionnaire [EQ-5D-5L], EuroQol visual analogue scale [EQ-VAS], pruritus numeric rating scale [NRS], medical outcomes study [MOS] sleep scale, and specific questions relating to past physician visits and financial burden), hospital discharge files, prescription drug files, and doctors' letters. Data are collected by treating physicians and site staff in electronic case report forms (eCRFs) and are checked for completeness and accuracy. Last prior AD treatment before baseline was defined as the last prior AD treatment that ended within 1 year of baseline data collection; if ≥ 2 prior AD treatments were given in parallel, each was regarded as the last prior AD treatment.

Statistical Analyses

All patients included in this analysis fulfilled the eligibility criteria, received ≥ 1 approved dose of dupilumab during the study, and had a documented baseline visit. There was no predefined hypothesis, and no formal statistical power calculation was performed. A sample size of 750 patients was sufficient for a 95% CI of [46.4%, 53.6%], assuming an estimated response rate of 50% (e.g., for EASI-75, $\geq 75\%$ improvement of the EASI score from baseline), and to detect rare adverse events with high likelihood.

Descriptive statistics are presented for all data. The number of non-missing data, means, standard deviations (SD), medians, and interquartile ranges were used as sample statistics.

Ethics Approval

This study was approved by the Ethics Committee at the University of Luebeck, Germany, and conducted in accordance with the Declaration of Helsinki, the guidelines for Good Epidemiological Practice, and all local regulatory guidelines. The patients in this manuscript have given written informed consent.

RESULTS

In total, 839 patients were assessed for eligibility, with 828 included in the study; of these, baseline data were available and analysed from 817 patients (Fig. 1) who all received the approved dosage of dupilumab at baseline. Patients were included from 126 study sites throughout Germany with 108 sites being office-based dermatological practices. Approximately half the patients were from large cities ($>$ 100,000 inhabitants; 52.4%); the remainder were from medium- (20,000–100,000 inhabitants; 26.2%) or small-sized (5000–20,000 inhabitants; 15.1%) cities, rural areas ($<$ 5000 inhabitants; 1.6%), or had missing data (4.8%).

Patient Demographics

Mean (SD) age of patients was 43.4 (15.8) years, and 396 (48.5%) patients were female (Table 1); the most common age category was 26 to 35 years (accounting for 25.0% of all patients; $n = 204$) (Supplementary Fig. 1). The proportion of patients with a BMI $> 30\ kg/m^2$ at baseline was 18.2%. Most patients were non-smokers (64.9%; Table 1). Secondary school diploma (10 years) was the most common highest level of education (32.6%), and most patients (53.9%) were in full-time employment (Table 1). Overall, 73.0% of patients had been treated for their AD > 6 months at the site of study inclusion.

Clinical Characteristics of Patients

AD clinical characteristics, according to Hanifin and Rajka [16], are presented in Table 2. Pruritus

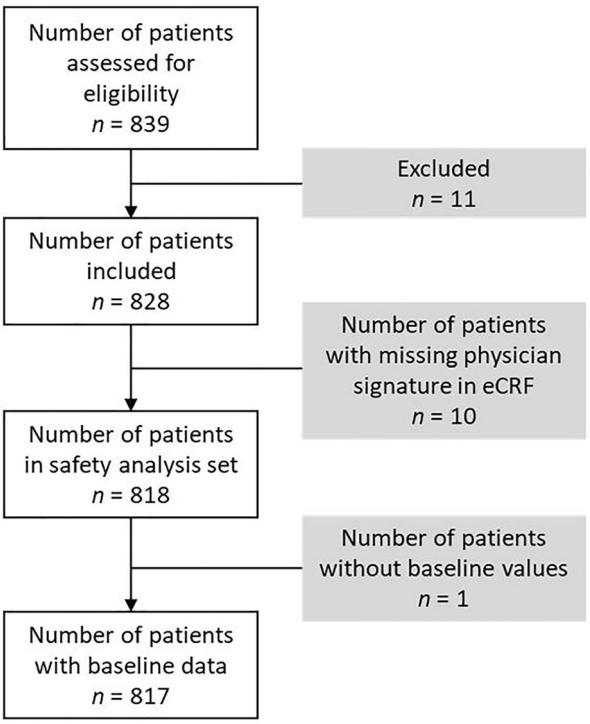

Fig. 1 Flow of patients through the PROLEAD study from eligibility assessment to baseline. *eCRF* electronic case report form, *n* number of patients

was the most common (99.6%), but all other characteristics had high prevalence. Overall, 66.6% of patients received their first diagnosis of AD during childhood. Total IgE levels were measured in 317 patients, with almost half (46.7%) having total IgE levels > 1000 kU/l. Pollen (54.1%) and house-dust mites (44.3%) were the most commonly reported sensitizations (Table 2).

Co-existing atopic and type 2 inflammatory diseases were present in 51.8% of patients, the most common being allergic conjunctivitis (36.8%) and bronchial asthma (22.5%). Cardiovascular comorbidities were present in 17.3%, with essential hypertension being the most frequent comorbidity (15.2%). Metabolic comorbidities were present in 8.9% patients, with type 2 diabetes being the most common (4.3%). Rheumatic diseases were present in 2.0%, with rheumatoid arthritis (0.6%) being most frequent. Psychological diseases were present in 7.5%, with depression (3.8%) the most common (Table 2). Mean (SD) age of patients with essential hypertension, type 2 diabetes, and depression was 60.0 (14.4), 61.1 (14.2), and 49.8 (13.1) years, respectively. In terms of patient family medical history, allergic rhinitis (45.8%), AD (40.4%), and asthma (26.3%) were the most commonly reported type 2 inflammatory diseases (Supplementary Table 1).

Burden of Disease

Mean (SD) number of patient-reported flares (exacerbations) in the past 12 months was 6.1 (9.1). Furthermore, in the past 24 months, mean (SD) number of nights spent in hospital as an inpatient was 2.1 (6.4), days spent in day care unit/hospital was 0.8 (4.9), and outpatient hospital admissions were 1.1 (3.5) (Supplementary Table 2). In the past 24 months, mean (SD) days receiving UV therapy was 5.3 (14.6).

AD presented a burden to patients' abilities to pursue and/or adhere to their education and profession. Overall, 50.7% of patients answered "very", "quite a bit", or "moderately" to the question, "To what extent does your AD hamper you currently in practising your profession/in your studies/in everyday school life?" (Fig. 2); moreover, 73.2% of patients were not working/studying for ≥ 1 day, and 20.2% were not working/studying for ≥ 10 days due to AD in the last 12 months. Furthermore, in the past 12 months, mean (SD) number of times patients visited a physician because of their AD was 8.2 (7.6) (Supplementary Table 3).

AD also poses a financial burden for many patients with a mean monthly spend of €56.96 for AD associated treatment, in addition to prescribed medications (Supplementary Table 3).

Prior and Concomitant Treatment for AD

Overall, 96.6% of recruited patients had previously received topical treatment, with TCS (94.6%) being the most frequent. In total, 61.4% of patients had received systemic therapy, with oral corticosteroids (OCS; 49.9%) being the most frequent and about 1/3 being previously treated with non-steroidal systemic immunosuppressants; 51.3% of patients had

Table 1 Baseline demographics, education, and employment status of patients (n = 817)

Characteristic	Mean	SD	Median	IQR	*n*
Age, years	43.4	15.8	41.0	30.0–55.0	817
Female	42.8	15.6	40.5	29.0–55.0	396
Male	43.9	15.9	41.0	31.0–55.0	421
Height, cm	172.7	8.9	172.0	167.0–179.0	807
Female	166.9	6.5	168.0	163.0–171.0	392
Male	178.0	7.2	178.0	173.0–183.0	415
Weight, kg	77.8	17.6	75.0	65.0–88.0	808
Female	71.7	17.5	69.0	60.0–80.0	393
Male	83.7	15.6	82.0	72.0–92.0	415
BMI, kg/m^2	26.0	5.3	25.0	22.5–28.7	807
Female	25.7	6.1	24.2	21.5–28.5	392
Male	26.3	4.3	25.7	23.2–28.7	415
	***n* = 817**				
Sex, % (n)					
Female	48.5 (396)				
Male	51.5 (421)				
Smoking behaviour, %					
Non-smoker	64.9				
Smoker	25.3				
Ex-smoker	9.6				
Missing	0.2				
Highest education, %					
Secondary school diploma (10 years[a])	32.6				
High school diploma (12/13 years[a])	26.7				
University degree	19.5				
Secondary school diploma (9 years[a])	16.2				
Missing	2.2				
Not answered	1.6				
Without graduation	1.4				
Employment status, %					
Employed	71.5				
Full-time	53.9				
Part-time	15.7				

Table 1 continued

Characteristic	Mean	SD	Median	IQR	*n*
Not answered	2.0				
Not employed[b]	25.3				
Missing	2.0				
Not answered	1.2				

BMI body mass index, *IQR* interquartile range, *n* number of patients, *SD* standard deviation
[a]Indicates the total number of years spent in school to obtain this diploma
[b]The criterion 'Not employed' could include patients who were students

previously received UV/phototherapy (Table 3). A total of 38.6% were systemic-naïve patients before receiving dupilumab.

In total, 83.1% of patients had received AD treatment and 9.2% (75/817) had not received any AD treatment in the 12 months prior to baseline. Overall, 43.6% of patients received only topical AD therapy in the 12 months before baseline, of which the most commonly reported at last visit before baseline were moderate potent (Class 2) and potent (Class 3) TCS. The most frequently reported systemic AD therapy was OCS (18.7%), and 13.6% of patients received UV/phototherapy at last visit prior before baseline (Table 3).

At baseline, topical AD therapy with Class 2 or Class 3 TCS was the most common concomitant treatment given in combination with dupilumab, although frequency varied among patients. In total, 1.6%, 0.6%, and 0.1% received OCS, ciclosporin A, or azathioprine in combination with dupilumab at baseline with mean doses of 23, 140, and 50 mg/day, respectively. Overall, 1.2% of patients received UV/phototherapy and 14.0% received systemic antihistamines in combination with dupilumab at baseline (Table 3). In contrast, 50.4% did not receive any AD treatment in combination with dupilumab at baseline.

When comparing AD treatment between last visit before baseline and baseline (in combination with dupilumab), the requirement for combined systemic and topical AD treatment per TCS class, as well as topical calcineurin inhibitor (TCI), was reduced by approximately 50% (Fig. 3A); most patients were switched from a previous systemic AD treatment to dupilumab without an overlap (Fig. 3B); UV/phototherapy and antihistamines were withdrawn in most patients (Fig. 3C).

Reasons for Initiation of Dupilumab

The most common reported reasons to initiate treatment with dupilumab were 'topical therapy alone was not sufficient' (95.1%) and 'due to the risk-benefit ratio' (42.3%) (Fig. 4). In terms of clinical eligibility criteria for systemic treatment as defined by the checklist for systemic treatment of AD (Supplementary Fig. 2A) [6], 85.4% of PROLEAD patients fulfilled these criteria (Supplementary Fig. 2B).

Physician- and Patient-reported Outcomes at Baseline

Physician- and patient-reported outcomes at baseline are presented in Table 4. The mean (SD) baseline EASI of 22.9 (14.5) represents patients with severe, bordering moderate AD [17] (Table 4). Taking prior AD treatment into account and defining patients with systemic treatment at the visit prior to baseline as having severe AD, most patients presented with severe AD (EASI > 21 and/or systemic AD treatment) at baseline (62.9%). Overall, 27.7% had moderate AD (EASI, 7.1–21), and 6.5% presented with EASI ≤ 7 at baseline. Other baseline physician-

Table 2 Patient clinical characteristics at baseline (n = 817)

Clinical characteristics	***n* = 817**		
Characteristics of AD by Hanifin and Rajka, %			
Pruritus	99.6		
Chronic or chronically relapsing dermatitis	86.1		
Typical morphology and distribution of eczema	85.3		
Personal or family history of AD	73.2		
First diagnosis of AD, %			
Childhood	66.6		
Adulthood	21.9		
Adolescence	11.5		
Total IgE, kU/l, n	n = 317		
$<$ 100	46		
$\geq$ 100–1000	23		
$>$ 1000	148		
Sensitizations, %	Yes	No	Unclear
Pollen	54.1	27.2	18.7
House-dust mites	44.3	37.0	18.7
Food	25.8	49.3	24.9
Mould	13.8	57.8	28.4
Other	25.2	38.2	36.5
	Prevalence	**Treated with medication**	
Co-existing atopic and type 2 inflammatory diseases, % (n)	51.8 (423)	NA	
Allergic conjunctivitis	36.8	17.4	
Other allergies (house dust mites, pollen, mould)	27.2	9.5	
Bronchial asthma	22.5	14.4	
Food allergy	17.3	1.6	
Chronic rhinosinusitis with or without nasal polyps	2.6	1.5	
Atopic conjunctivitis	2.2	1.7	
Eosinophilic esophagitis	0.2	0.1	
Cardiovascular comorbidities, % (n)	17.3 (141)	NA	
Essential hypertension	15.2	13.7	
Peripheral arterial disease	1.2	1.2	
Coronary heart disease	1.1	1.0	

Table 2 continued

	Prevalence	Treated with medication
Heart failure	0.7	0.7
Cerebrovascular disease	0.2	0.2
Thrombosis/thromboses	0.2	0.2
Metabolic diseases, % (*n*)	8.9 (73)	NA
Type 2 diabetes	4.3	3.2
Hyperuricaemia	2.3	1.1
Lipid metabolic disorder	2.6	1.5
Metabolic syndrome	1.0	0.4
Liver diseases, % (*n*)	1.0 (8)	NA
Liver cirrhosis	0.4	0.1
Chronic hepatitis/increased transaminases	0.4	0
Non-alcoholic steatohepatitis	0.2	0
Gastrointestinal diseases, % (*n*)	2.8 (23)	NA
Gastric ulcers	0.6	0.2
Renal diseases, % (*n*)	2.0 (16)	NA
Renal insufficiency	0.7	0.4
Pulmonary diseases, % (*n*)	6.5 (53)	NA
Chronic bronchitis	1.1	0.9
Rheumatic diseases, % (*n*)	2.0 (16)	NA
Rheumatoid arthritis	0.6	0.2
Psychological diseases, % (*n*)	7.5 (61)	NA
Depression	3.8	2.0

Proportionate data were calculated using a total of 817 patients unless otherwise specified
AD atopic dermatitis, *IgE* immunoglobulin E, *n* number of patients, *NA* not applicable

and patient-reported outcome disease scores are presented in Table 4.

DISCUSSION

The findings of this prospective, non-interventional study describe real-world demographics and characteristics of German patients with AD receiving treatment with dupilumab, using a relatively large sample size for this population. The 126 study sites covered a wide distribution of the use of dupilumab throughout Germany, and there was an equal distribution between sites in large cities compared to sites in medium- and small-sized cities or rural areas. Data on the effectiveness and safety of dupilumab in this patient population will be reported in a future publication. Most patients in PROLEAD had received numerous treatments before initiation of dupilumab but many nevertheless

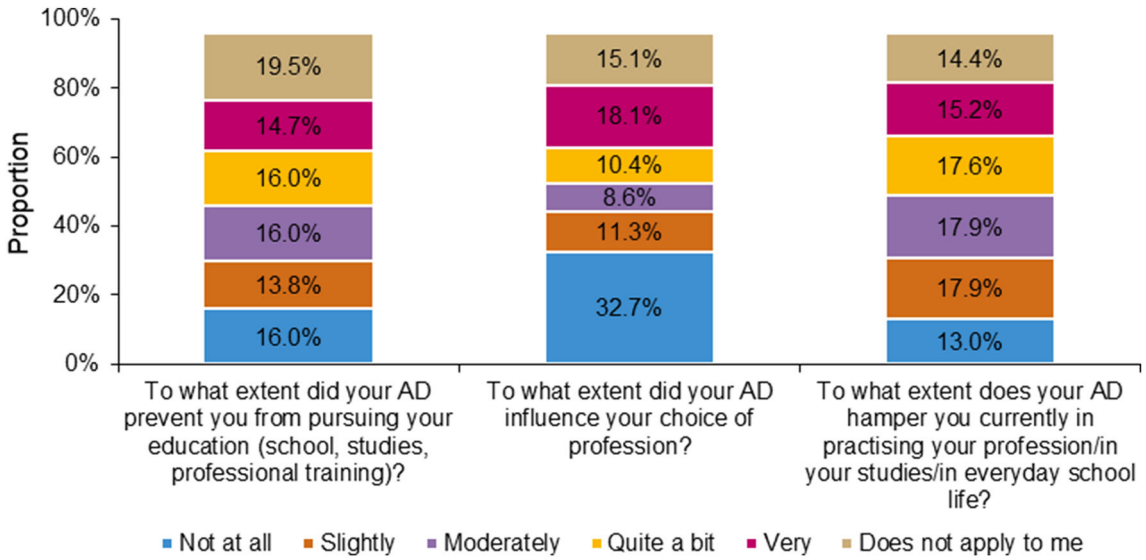

Fig. 2 Burden and impact of AD on patients' education and profession (n = 817). *AD* atopic dermatitis, *n* number of patients

Table 3 Previous and concomitant treatment for AD (n = 817)

	AD treatment ever before in life (%)	Last prior AD treatment before baseline within the last 12 months (%)	Concomitant AD treatment at baseline in combination to dupilumab (%)
TCS class 1	47.2	16.5	7.3
TCS class 2	72.7	41.9	22.9
TCS class 3	75.2	46.0	22.8
TCS class 4	35.4	10.9	3.8
TCI	46.9	20.4	10.0
OCS	49.9	18.7	1.6
Ciclosporin A	28.5	12.6	0.6
Methotrexate	3.5	1.1	0
Azathioprine	1.3	0.1	0.1
Mycophenolate mofetil	0.4	0	0
Antihistamines	60.2	29.3	14.0
UV/phototherapy/PUVA	51.3	13.6	1.2

AD atopic dermatitis, *OCS* oral corticosteroids, *PUVA* psoralen long-wave ultraviolet A, *TCI* topical calcineurin inhibitors, *TCS* topical corticosteroids, *UV* ultraviolet

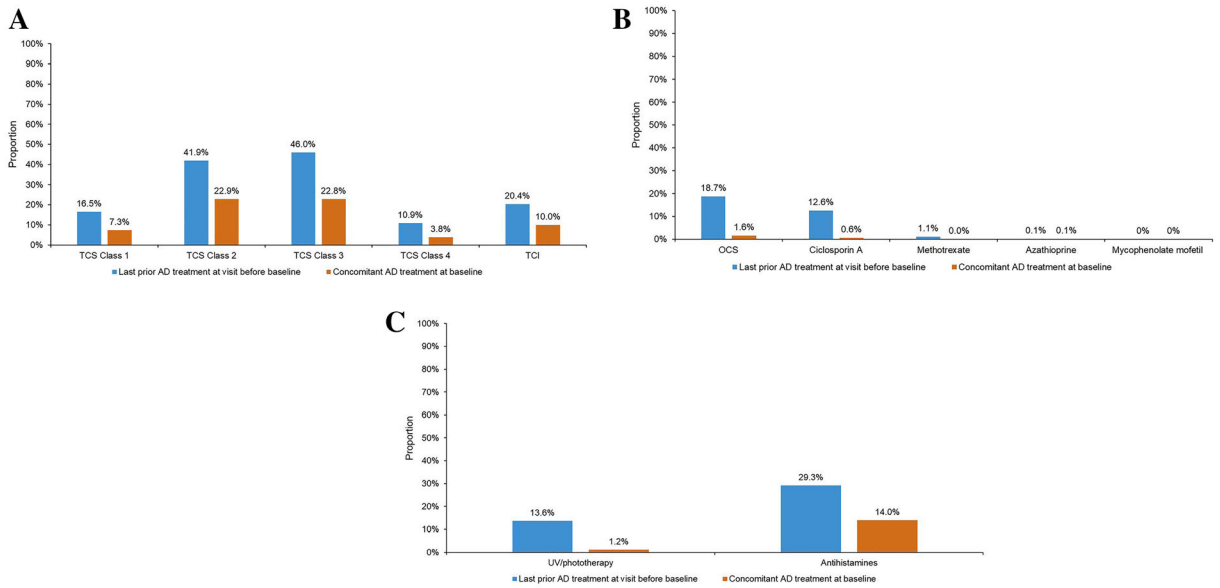

Fig. 3 Proportion of patients with prior and concomitant AD treatment at baseline: **a** topical therapy; **b** systemic therapy; **c** UV/phototherapy and antihistamine treatment (all $n = 817$). *AD* atopic dermatitis, *n* number of patients, *OCS* oral corticosteroids, *TCI* topical calcineurin inhibitors, *TCS* topical corticosteroids, *UV* ultraviolet

presented with AD-related signs and symptoms as well as impaired QoL. The most common prior topical therapy (within 12 months prior to baseline) was Class 3 TCS and the most common prior systemic treatment was OCS. This reflects the results from the recent German claims-based analysis by Hagenström et al. (2021), which included data from general practitioners, paediatricians, and internists, as well as dermatologists [5]. However, the number of patients receiving topical and/or systemic treatments for AD decreased towards baseline, with approximately half then receiving dupilumab as monotherapy. Moreover, patients receiving dupilumab became less dependent on combination therapy with systemic and topical AD treatment over time. Although combination therapy use reduced with dupilumab, the updated S2k guidelines for systemic treatment recommends that dupilumab is used in combination with a topical anti-inflammatory treatment, as part of a four-step regimen [6]. PROLEAD patients treated with conventional systemic therapies at last prior visit were generally switched to dupilumab without overlap. Although not widely implemented in this study, previous publications have recommended an overlap as practical management for patients transitioning from conventional systemic treatments to dupilumab, as concurrent treatment with these therapies does not alter either drug's intrinsic risk profile [10]. The proportion of patients with previous and concomitant treatment with antihistamines was unexpectedly high, as there is no evidence for the treatment of pruritus in AD patients and they are not recommended by treatment guidelines. No patients were receiving methotrexate as concomitant medication, potentially as it is not licensed in this indication. Most patients reported that AD either 'slightly' or 'moderately' hampered their profession/studies/everyday school life; however, a similar proportion of patients reported that AD affects their everyday life in varying degrees, from 'not at all'/'does not apply to me' to 'quite a bit'/'very'.

Data from this study indicate that patients in the real-world are less severely affected by AD than those who participated in the pivotal phase III CHRONOS trial in terms of skin lesions at baseline, but not in terms of symptoms or QoL [12]. It should be noted, however, that the CHRONOS study excluded patients who had

Table 4 Physician- and patient-reported outcome disease scores for signs, symptoms, and quality of life at baseline (n = 817)

	Mean	SD	Median	IQR	*n*
Physician-reported outcomes					
EASI	22.9	14.5	20.2	12.0–31.2	786
BSA, %	44.4	25.9	50.0	23.0–64.0	814
SCORAD	63.3	16.2	64.1	52.3–75.5	814
SCORAD Sleeplessness	5.5	3.1	6.0	3.0–8.0	814
SCORAD Pruritus	7.2	2.3	8.0	6.0–9.0	814
IGA	3.3	0.7	3.0	3.0–4.0	813
Patient-reported outcomes					
POEM	20.4	6.3	21.0	16.0–25.0	785
DLQI	13.9	7.1	13.0	8.0–19.0	800
EQ-5D-5L	0.8	0.2	0.9	0.8–0.9	791
EQ-VAS	55.1	20.9	55.0	40.0–70.0	793
Average Pruritus NRS (during last 24 h)	6.4	2.4	7.0	5.0–8.0	799
Peak Pruritus NRS (during last 24 h)	7.4	2.3	8.0	6.0–9.0	791
MOS Sleep Problems Index I	43.6	13.3	43.3	33.3–53.3	798
MOS Sleep Problems Index II	48.2	19.5	47.8	33.9–62.8	801

BSA body surface area, *DLQI* dermatology life quality index, *EASI* eczema area and severity index, *EQ-5D-5L* five-level EuroQol five-dimensional questionnaire, *EQ-VAS* EuroQol visual analogue scale, *IGA* Investigator's global assessment, *MOS* medical outcomes study, *n* number of patients, *NRS* numeric rating scale, *POEM* patient-oriented eczema measure, *SCORAD* SCORing atopic dermatitis

received TCS or TCIs within 1 week before baseline or immunosuppressive/immunomodulating drugs or phototherapy for AD within 4 weeks before baseline [12]. Interestingly, disease-specific DLQI scores at baseline among the 800/817 patients who completed the questionnaire were higher (mean, 13.9 [7.1]; indicating a large impact on QoL) than those reported for patients with chronic hand eczema included in the German CARPE registry (mean, 8.8, SD 6.3) [18, 19], supporting a high burden of AD in the PROLEAD population. In recent years, PROs have been used in real-world clinical practice as well as in clinical trials and provide an important compliment to clinician-reported outcomes to support decision making [20]. The high baseline DLQI scores are explained by most severe cases of AD receiving dupilumab initially, whereas in later years, physicians would increasingly prescribe dupilumab for moderate AD, following the implementation of dupilumab in routine clinical care. Conversely, the mean (SD) DLQI scores in the present study (13.9 [7.1]) were more similar to those reported in the PsoBest registry (12.4 [3.4]) [21, 22]. Consistently, the physician- and patient-reported severity and burden of AD in PROLEAD were also greater than those reported in the TREATgermany AD registry and prospective, observational, European-wide EUROSTAD study, as indicated by mean respective EASI (22.9 vs. 16.1 vs. 16.2, respectively), SCORAD (63.3 vs. 40.96 vs. not reported), Peak Pruritus NRS (7.4 vs. not reported vs. 5.5), DLQI (13.9 vs.

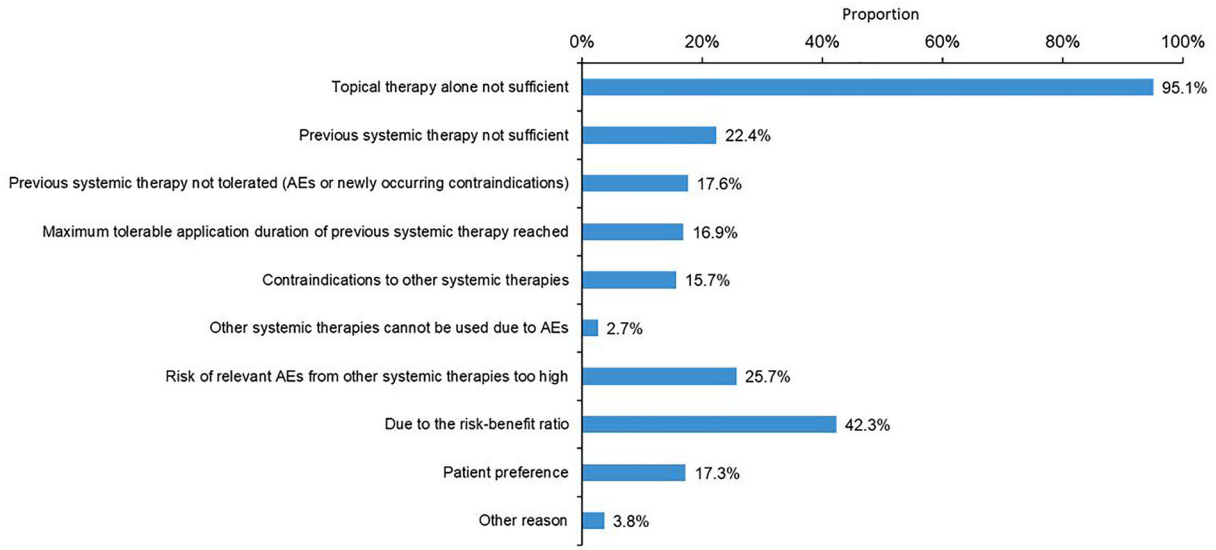

Fig. 4 Reasons to initiate treatment with dupilumab (n = 817). *AE* adverse event, n number of patients

11.8 vs. 11.8), and POEM (20.4 vs. 16.8 vs. 17.0) scores [23, 24]. Mean IGA scores in PROLEAD (3.3) were comparable to those in EUROSTAD (3.1) [24]. The results of the present and previous studies investigating dupilumab demonstrate the potential to improve management of moderate-to-severe AD.

The rate of co-existing atopic and type 2 inflammatory diseases at baseline was lower in patients included in PROLEAD (51.8%) than in patients treated with dupilumab in CHRONOS (62%) [12]. Additionally, co-existing type 2 inflammatory diseases are most common in patients who receive systemic AD treatment with dupilumab in contrast to other comorbidities, such as rheumatic or metabolic diseases, which are common clinical manifestations in patients with psoriasis [25]. Zander et al. reported that patients with AD in medical history (n = 5883) frequently present with type 2 inflammatory diseases (allergic conjunctivitis: 42.0%; allergic asthma: 17.2%), consistent with the results of PROLEAD (allergic conjunctivitis: 36.8%; bronchial asthma: 22.5%), highlighting the requirement for comprehensive, dermatologically-guided diagnostics in AD to ensure patients receive suitable therapy [26].

Reassuringly, the demographic characteristics of the PROLEAD patient population were consistent with those in the TREATgermany AD registry and AtopicHealth healthcare study of atopic dermatitis in Germany [23, 27, 28]. The TREATgermany registry reported that most patients with AD have an education level of secondary school diploma (37.2%) and are in full-time employment (73.2%), which is comparable to the findings from PROLEAD (Table 1). Comorbidities were also similar between the TREATgermany and PROLEAD patient populations [23].

Interestingly, the most important reason to initiate treatment with dupilumab was that topical therapy alone was insufficient. This attribute has been recently added to step 4 in the four-step therapeutic regimen figure according to AD severity in the updated S2k guideline, "Systemic treatment of atopic dermatitis" for when systemic treatment should be initiated [6]. However, the efficacy and safety of dupilumab presents the potential for inclusion as a possible step 3 option, which describes treatment approaches for moderate eczema. Inclusion of systemic therapy in future guideline updates for treatment of moderate AD might address the unmet need for therapeutic innovations to alleviate the lack of improvement in

the quality of care for AD in Germany, as reported by several studies, including AtopicHealth, a national health care study [27–29].

This guideline publication [6] also lists the checklist to identify patients with moderate-to-severe AD who require systemic treatment. More than 85% of PROLEAD patients fulfil the criteria in all three sections at baseline, with almost all patients fulfilling the sections for relevant objective severity and lack of treatment response. This finding is a reverse validation of the checklist, showing that most patients receiving systemic treatment in this study would have been identified with the checklist as needing such treatment, making it a valuable tool for patient identification.

CONCLUSIONS

The results from PROLEAD describe that patients treated with dupilumab present with moderate to severe AD, a median age of 41.0 years, with no difference between sex, and a prevalence of pruritus. The disease burden is further increased in approximately half the patients by the presence of co-existing type 2 inflammatory diseases, notably allergic conjunctivitis and asthma.

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Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author or Mike Bastian (mike.bastian@sanofi.com) on reasonable request.

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