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ORIGINAL ARTICLE

Baseline characteristics, disease severity and treatment history of patients with atopic dermatitis included in the German AD Registry TREATgermany

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Abstract

Background The Atopic Dermatitis (AD) TREATgermany registry was initiated by the German Society for Dermatology (DDG) in 2011 to evaluate the 'real-life' situation of health care for patients with AD.

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Objectives Interim data analysis on baseline characteristics as well as current and prescribed systemic treatments of the TREATgermany registry patients.

Methods Patients (≥18 years) with moderate-to-severe AD [objective (o)SCORAD > 20], or with current or previous anti-inflammatory systemic treatment for AD within 24 months, were included and are followed up over at least 24 months. To assess clinical signs, the eczema area severity index (EASI, 0–72), the oSCORAD (0–83) and the Investigator Global Assessment (IGA; 6-point scale) were used. The disease severity was globally scored by the patients [Patient Global Assessment (PGA); six-step Likert scale]. Disease symptoms were assessed by the patient-oriented eczema measure (POEM, 0–28) and numeric rating scales (NRS, 0–10). Health-related quality of life was measured using the dermatological life quality index (DLQI, 0–30).

Results A total of 612 patients were recruited across 32 sites between 06/2016 and 01/2019 (mean age: 42.6 ± 14.2 years; mean oSCORAD: 40.8 ± 16.3). The mean POEM score was 16.3 ± 7.5. Pruritus was rated highest among subjective symptoms (NRS: 5.4 ± 2.7). The mean DLQI value was 11.3 ± 7.5. The frequency of arterial hypertension was lower (20.8%) compared with the general population, whilst this was higher for depression (10%). More than 60% of the patients had received systemic glucocorticosteroids, and 36.8% had received cyclosporine A prior to inclusion. Dupilumab was the leading substance documented as either 'current' (12.1%) or 'prescribed' (31.4%) at baseline.

Conclusions These 'real-life' data clearly demonstrate the substantial disease burden. Most of TREATgermany patients were already treated with or prescribed dupilumab at baseline. Moreover, current findings indicate the urgent need for further alternative agents in order to achieve a perceptible improvement of quality of life of patients with moderate-to-severe AD.

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Conflicts of interest

Annice Heratizadeh received lecture and/or consultancy fees from LEO Pharma, Novartis, Pierre Fabre, Sanofi Genzyme, Beiersdorf, Hans Karrer, Nutricia and Meda. The Center for Evidence-Based Health Care at TU Dresden receives institutional support for self-designed scientific studies from ALK, Novartis, Pfizer and Sanofi. Susanne Abraham received lecture and/or consultancy fees from Novartis, LEO Pharma, Lilly, Sanofi, Beiersdorf and AbbVie. Andreas Wollenberg has received institutional research grants from Leo Pharma; has attended advisory boards or performed consultancies for AbbVie, Chugai, Galapagos, Galderma, Incyte, LEO Pharma, Lilly, MedImmune, Novartis, Regeneron and Sanofi-Genzyme; has lectured at educational events sponsored by Chugai, Galderma, LEO Pharma, Lilly, MedImmune, Novartis, Pfizer, Regeneron and Sanofi-Genzyme; and his institution is involved in performing clinical trials with many pharmaceutical industries that manufacture drugs used for the treatment of psoriasis and atopic eczema. Margitta Worm has received honoraria or consultation fees from ALK-Abelló Arzneimittel GmbH, Mylan, Germany GmbH, Leo Pharma GmbH, Sanofi-Aventis Deutschland GmbH, Regeneron, Pharmaceuticals, Inc., and DBV Technologies S.A and participated in a company-sponsored speaker's bureau from ALK-Abelló Arzneimittel GmbH, Mylan Germany GmbH, Bencard Allergie GmbH, Novartis AG, Biotest AG, Actelion Pharmaceuticals Deutschland GmbH, Sanofi-Aventis Deutschland GmbH and HAL Allergie GmbH. Alexander Zink has been an advisor for and/or received speaker's honoraria from Beiersdorf Dermo Medical GmbH, Miltenyi Biotec GmbH, Novartis Pharma GmbH and Sanofi Genzyme. Ralph von Kiedrowski is a member of advisory boards, speaker and performs clinical studies with AbbVie, ALK Scherax, Almirall Hermal, Biofrontera, Biogen, BMS, Boehringer Ingelheim, Celgene, DermaPharm, Foamix, Gilead, Hexal, Janssen-Cilag, LEO, Lilly, Meda, Medac, Menlo, MSD, Novartis, Dr. R. Pfleger, Pfizer, Regeneron, Sanofi, Stallergens, Stiefel GSK, Tigercut and UCB. Michael Sticherling is a member of advisory boards, speaker and performs clinical studies with Sanofi GmbH and Novartis Pharma. Thomas Bieber has been lecturer and consultant for Regeneron and Sanofi/Genzyme. Bernhard Homey has received institutional research grants from Galderma, LEO Pharma and Novartis; has performed consultancies for Galderma, AbbVie, Janssen, Celgene, Sanofi-Genzyme, Regeneron, LEO Pharma and Novartis; he has also lectured at educational events sponsored by Galderma, AbbVie, Janssen, Celgene, LEO Pharma and Novartis; and is involved in performing clinical trials with many pharmaceutical industries that manufacture drugs used for the treatment of psoriasis and atopic eczema. Uwe Schwichtenberg received salary, was investigator, participated in advisory boards, acted as

speaker, and/or stockholder for AbbVie Deutschland GmbH, Almirall Hermal GmbH, Astellas Pharma GmbH, Beiersdorf Dermo Medical GmbH, Celgene GmbH, Janssen Cilag GmbH, Johnson & Johnson GmbH, LEO Pharma GmbH, L'Oréal GmbH, MEDA Pharma GmbH, Medical Project Design GmbH, Merz Pharmaceuticals GmbH, MSD SHARP & DOHME GmbH, Novartis Pharma GmbH, and Pfizer GmbH. Martin Mempel has obtained speaker's fees from Sanofi. Stefan Beissert received speaker honorarium and travel reimbursement by Sanofi. Tilo Biedermann gave advice to or got a honorarium for talks or research grant from the following companies: Mylan, Novartis, Sanofi, ALK, Sanofi-Genzyme, Alk-Abelló, Regeneron and Lilly. Stephan Weidinger is a co-principal investigator of the German Atopic Eczema Registry TREATgermany. He has received institutional research grants from Novartis, Pfizer and L'Oreal; has performed consultancies for Sanofi-Genzyme, Regeneron, LEO Pharma, Incyte and Novartis; he has also lectured at educational events sponsored by Sanofi-Genzyme, Regeneron, LEO Pharma, AbbVie and Galderma; and is involved in performing clinical trials with many pharmaceutical industries that manufacture drugs used for the treatment of psoriasis and atopic eczema. Jochen Schmitt received institutional grants from Novartis, Pfizer and Sanofi for investigator-initiated research, and honoraria for consultations from Sanofi and Novartis and industrial funding for investigator-initiated trials from Novartis, Sanofi and Pfizer. Thomas Werfel is a co-principal investigator of the German Atopic Eczema Registry TREATgermany. Thomas Werfel has received institutional research grants from LEO Pharma and Novartis; has performed consultancies for AbbVie, Janssen, Galderma, LEO, Sanofi-Genzyme and Novartis; he has also lectured at educational events sponsored by AbbVie, Janssen, Celgene, Galderma, LEO Pharma, Sanofi and Novartis; and is involved in performing clinical trials from various pharmaceutical industries that manufacture drugs used for the treatment of and atopic dermatitis.

Introduction

Atopic dermatitis (AD) represents a common chronic inflammatory skin disease affecting 1–7% of adults in Western industrialized countries.[1,2] In Germany, adults account for 60% of all AD patients.[3] Various factors, such as inhalant and food allergens, can potentially trigger skin inflammation and exacerbate AD, dependent upon complex genetic predispositions.[4–7] Subjective symptoms, namely pruritus and sleep disorders, represent key symptoms of AD. These have been demonstrated to lead to a substantial impairment of quality of life (QoL)[8,9] and are associated with an increased risk of psychiatric comorbidities.[10,11] Accordingly with AD patients reporting a loss in productivity,[12] health-economic analyses indicate this chronic skin disease has a high socio-economic impact.[13] Insufficient therapy efforts combined with a high willingness to pay[14] might further promote the usage of ineffective alternative treatments, particularly in patients with severe, highly chronic AD. Thus, the healthcare data clearly demonstrate there is a need for more effective care and better implementation of the national guideline in Germany.[9,15]

Ground-breaking developments in the field of systemic therapy might pave the way for an improvement of local health care in treating AD. Since its authorization in February and September 2017, dupilumab has provided a new first-line treatment option for patients with moderate-to-severe AD in the United States and in Europe. Data from the corresponding phase II and phase III studies clearly indicate beneficial treatment effects with a significant improvement of clinical signs, symptoms and quality of life in patients with moderate-to-severe AD, with sustained improvements observed over a period of 2 weeks to 1 year.[16–19]

However, in addition to findings from randomized placebo-controlled studies, data from routine care are generally necessary to evaluate the 'real-life' situation of health care for patients with AD. To address this, in 2011 the German Atopic Dermatitis TREATgermany registry was initiated as the world's first AD registry by the German Society for Dermatology (DDG).[20] Until 2015, TREATgermany was exclusively focused on severely diseased AD patients (TREATeczema). However, after a relaunch in May 2016, the TREATgermany registry was extended to patients with moderate AD. Since then, more than 600 patients have been recruited into the new version of the registry ('TREATgermany'). Here, we provide first results obtained from an interim data analysis of the TREATgermany registry focusing on baseline characteristics and current and prescribed systemic treatments of the TREATgermany registry patients.

Patients and methods

The TREATgermany registry is a prospective clinical nationwide multicentre registry that has formally been approved by the Medical Faculty of the Carl Gustav Carus University, Dresden, Germany (No. EK 118032016), and the responsible local ethics committees at the other participating sites. Patients are recruited at university and non-university hospitals as well as at dermatological practices. All dermatologists in Germany may participate, and new recruiting sites are continuously initiated (www.treatgermany.org).

Here, we performed a first interim data analysis on baseline characteristics and current and prescribed systemic treatments of the TREATgermany registry patients.

Inclusion criteria

Patients aged ≥18 years diagnosed with AD according to the UK working party diagnostic criteria[21,22] are serially included from dermatological routine care. The severity of AD must be moderate to severe as defined by objective SCORAD[23] (>20 points), or currently receiving anti-inflammatory systemic treatment for AD, or having received anti-inflammatory systemic treatment for AD within 24 months of inclusion. Patients who had been enrolled into the previous AD registry TREATeczema may be enrolled into TREATgermany following informed consent, provided if they meet the above inclusion criteria.

Objectives of the TREATgermany registry

The main objectives of this national evidence-based clinical registry and research network are (i) characterizing medical care and pharmaceutical therapies of adults suffering from moderate-to-severe AD; (ii) evaluating the perspective of the patient (utility, treatment goals, quality of life and treatment satisfaction), sequence of treatments and change in treatments; and (iii) investigating comparative effectiveness, tolerability and safety of systemic therapies for moderate-to-severe AD. Additionally, TREATgermany aims to represent a platform for further investigations, such as pragmatic clinical trials, epidemiologic studies, outcomes research, and immunologic and molecular research (given approval of responsible ethics commission).

Schedule of assessments and measuring instruments

A particular focus of this registry has been placed on characterizing medical care, the effectiveness of pharmaceutical therapies and the corresponding perspective of moderately to severely diseased AD patients in a longitudinal manner. Therefore, after oral and written informed consent, enrolled patients are prospectively followed up for a period of at least 24 months. During this observation period, standardized study visits are performed to document patient characteristics, clinical data, patient-reported outcomes, physician's reasons for treatment decisions and patient satisfaction based on validated questionnaires. These are completed by the patient and the physician during routine care visits in the clinic or practice. Every visit is completed by a routine dermatological examination.

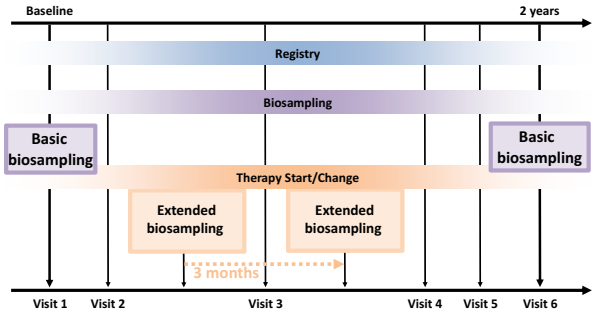

Figure 1 Time schedule of assessments of the TREATgermany registry.

The first study visit is scheduled at patient inclusion (baseline visit; V1). The second and third study visits are scheduled three and 6 months after baseline, respectively. Thereafter, study visits are scheduled after 3 months (if a new systemic treatment was initiated) or 6 months (where no new systemic treatment was prescribed; Fig. 1).

For all assessments, the use of validated instruments is considered. According to the recommendations of the Harmonizing Outcome Measures for Eczema (HOME) initiative,[24–26] target parameters to evaluate the effectiveness of AD treatment in clinical trials include the physician-assessed clinical severity of signs, disease symptoms, quality of life and long-term control of AD. To assess clinical signs, the eczema area severity index [EASI] and the oSCORAD[27,28] are used. With regard to recent publications, a cut-off level of seven points was applied for the EASI, whilst this was 24 points for the oSCORAD for identification of patients with moderate-to-severe AD for this interim analysis.[29,30] Disease symptoms are assessed by the patient-oriented eczema measure (POEM) and numeric rating scales (NRS)[31,32] for pruritus, pain and sleeping problems. Concerning the latter, the patients are asked whether they were prevented from sleeping. Moreover, the disease severity is globally scored by both the physician and the patient, applying the Investigator Global Assessment (IGA; 6-point scale; 0 = no clinical signs, 5 = very severe erythema/papules/infiltrate with crusting/oozing) and the Patient Global Assessment (PGA; 6-point scale; 0 = complete resolution, 5 = very severe), respectively. Furthermore, the disease control (totally/well-controlled weeks),[33] health-related quality of life (dermatological life quality index, DLQI), the patients' and physicians' treatment satisfaction and physicians' reasons for the choice of specific interventions are also assessed.[34]

In addition, participants are given the option to consent to the donation of biosamples for the purposes of molecular research towards identification of disease biomarkers, disease progression and response to therapy. Biological samples are collected at baseline and at month 24 (EDTA, PAXgene blood RNA, serum, stool, skin swabs), and before and 3 months after initiation of a new systemic therapy (EDTA, PAXgene blood RNA, serum, stool, skin swabs, lesional and non-lesional skin biopsy). Sample generation and transfer are highly standardized and monitored regularly. Samples are preprocessed and stored through the P2N biobanking infrastructure in compliance with relevant data protection requirements and ethical principles.[35]

Adverse events and reasons for withdrawals are documented according to the requirements of the declaration of Helsinki and 'Good clinical practice' (GCP).

Data management and statistical analysis

The demographic data, disease course and severity, medical care, pharmaceutical treatment of AD and the remaining assessments

mentioned above are electronically documented using CE-certified software solutions (ESPRIO, Seracom Software Solutions GmbH, Stuttgart, Germany and REDCap, Research Electronic Data Capture; REDCap 8.5.28 ©2019 Vanderbilt University, Nashville, TN, USA). Alternatively, a patient and physician report form can be completed by pen and paper upon request. Pseudonymized data are sent to and stored at the registry data centre at the Center for Evidence-Based Health Care at Dresden University Hospital (ZEGV Dresden).

The data from patients previously enrolled in TREATeczema (about 80 patients) may be transferred into TREATgermany following informed consent.[20] Descriptive and exploratory data analyses are performed at least once per year by the ZEGV Dresden.

In order to estimate the number of patients necessary to determine the comparative effectiveness of systemic therapies for severe AD in adults, the detectable difference ('detectable alternative') was calculated for different scenarios. Assuming an oSCORAD-50 response rate of 50% (i.e. 50% of treated patients have a ≥50% improvement of oSCORAD) under a particular treatment (e.g. cyclosporine) differences of 27%, 19% and 14%, respectively, in oSCORAD-50 response rate can be shown with a statistical power of 80% and $\alpha = 5\%$ having $n = 50$, $n = 100$, $n = 200$, respectively, patients in every treatment group (PS Power and Sample Size Calculations version 2.1.30).

These calculations revealed that at least 600 patients should be enrolled. This dimension of study is assumed to be adequate for imaging medical care and medical treatment of patients with moderate-to-severe AD.

The data are checked for plausibility at the operational head office in Dresden. Any incomplete or implausible data are queried with the concerned recruiting centre. On-site monitoring of the recruitment centres is carried out every 2 years. Detailed aspects to be verified are defined in a monitoring manual. Data analysis is descriptive and explorative. Differences in means of measured variables are examined using *t*-test and Mann–Whitney *U*-test. Frequencies are examined using the chi-square test and Fisher's exact test. More complex questions, particularly on changes in parameters over time, are answered by multivariate analyses using regression models or methods of variance analysis as appropriate.

Here, we report on the baseline characteristics of all patients enrolled in TREATgermany up until January 2019.

Results

Number of patients and general patient characteristics

A total of 612 patients recruited across 32 sites (16 dermatological clinics and 16 dermatological practices) were enrolled in the TREATgermany registry from June 2016 to January 2019.

Table 1 provides an overview of the patients' demographic data including comorbidities and further specific information from the medical history at baseline. The mean age of the TREATgermany population was 42.6 ± 14.2 years, with females accounting for 38.2% of the cohort. Almost half of the TREATgermany patient population had received higher education. With regard to allergies, allergic sensitizations to mould and food allergens were most often documented, whilst clinically

Table 1 General patient characteristics at baseline

	n	%
	612	**100**
Age in years (mean ± SD) n_{total} = 606	42.6 ± 14.2	
Gender (female) n_{total} = 602	230	38.2
Level of education n_{total} = 601		
Without graduation	5	0.8
Certificate of secondary education	71	11.8
General certificate of secondary education	235	39.1
General qualification for university entrance†	145	24.1
Graduate degree	145	24.1
Allergic sensitization		
Pollen n_{total} = 593		
Yes	111	18.7
No	439	74.0
Unclear	43	7.3
House dust mite n_{total} = 593		
Yes	139	23.4
No	401	67.6
Unclear	53	8.9
Food n_{total} = 593		
Yes	242	40.8
No	231	39.0
Unclear	120	20.2
Mould n_{total} = 592		
Yes	268	45.3
No	186	31.4
Unclear	138	23.3
Allergic comorbidity (*n* = 612)		
Bronchial asthma	273	44.6
Allergic rhinitis	409	66.8
Other non-allergic comorbidities (referred to 612 registry patients)		
Arterial hypertension	127	20.8
Depression	61	10.0
Type II diabetes mellitus	20	3.3
History of myocardial infarction	4	0.7
Morbus Crohn/Colitis ulcerosa	9	1.5
Renal insufficiency	6	1.0
Condition after stroke	1	0.2
Cardiac insufficiency	2	0.3
Diabetes type I	1	0.2
Rheumatoid arthritis	2	0.3
Further specific details from the medical history		
Herpes infection in the past n_{total} = 353	83	23.5
Skin cancer in the past (*n* = 612)	2	0.3

†Corresponding to high school diploma or A level.
Green: information from patient's questionnaires; white: information from physician's questionnaire.

relevant respiratory allergy (as assessed by a physician) was recorded in 44.6% (bronchial asthma) and 66.8% (allergic rhinitis) of the patients. Regarding other frequent comorbidities, arterial hypertension (20.8%) and depression (10%) were also reported. The physician-documented prevalence of further comorbidities ranged between 3.3% and 0.2%. A particular focus was placed on potential contraindications for cyclosporine A treatment. Here, 149 patients (24.3%) reported arterial hypertension or renal insufficiency, skin cancer or PUVA therapy in the past. Finally, history of extensive herpes infection (i.e. eczema herpeticum) was proactively investigated since December 2017 in a subgroup of 353 patients, and 23.5% (n = 83) of these confirmed having such a history of herpes infection.

In more detail, a percentage of 86.7% (n = 72) of patients with a positive history of eczema herpeticum reported ever having received systemic treatment of AD before baseline, whilst only 13.3% (n = 11) of patients with eczema herpeticum did not have any systemic treatment of AD in the past.

Severity of AD at baseline

Details on the severity of the disease as assessed by the patients and the physicians are described in Table 2. According to the inclusion criteria defined for the registry, the vast majority of the patients suffered from moderate-to-severe AD at baseline (as assessed by IGA 3–5: 76.7%; oSCORAD ≥ 24: 85.1%; EASI > 7: 71.9%). Regarding the global severity of AD, there was a clear trend for the patients themselves to score their AD as less severe when compared to the physicians (Fig. 2), resulting in a significant difference in scoring (Person's chi-squared test, $P < 0.01$). Specifically, 76.8% of physicians scored the severity of AD as moderate, severe or very severe, compared with 67.4% of patients. The disease severity assessed by IGA and PGA did not depend on sex of patients (IGA: chi-squared test: $P = 0.454$; PGA: chi-squared test: $P = 0.422$).

Table 2 Baseline information on the disease severity of AD

Disease severity at the time of enrolment	n	%
Investigator's Global Assessment (0–5) n_{total} = 607		
Clear/mild/(almost) resolved (0–2)	141	23.2
Moderate (3)	237	39.0
Severe/very severe (4–5)	229	37.7
Patient's Global Assessment (0–5) n_{total} = 598		
Clear/(almost) resolved/mild/(0–2)	195	32.6
Moderate (3)	182	30.4
Severe/very severe (4–5)	221	37.0
Eczematous lesions present at...		
Face n_{total} = 600	482	80.3
Hands n_{total} = 600	466	77.7
Feet n_{total} = 600	298	49.7
Genital area n_{total} = 600	102	17.0
Flexures (inquired since 2018) n_{total} = 359	277	77.2
Neck (inquired since 2018) n_{total} = 359	289	80.5
Clinical signs	**n**	**Mean ± SD**
Body surface area (BSA)	571	18.4% ± 21.7%
oSCORAD	604	40.8 ± 16.3
oSCORAD < 24	90 (14.9%)	
oSCORAD ≥ 24	514 (85.1%)	
EASI	605	15.8 ± 12.6
EASI ≤ 7	170 (28.1%)	
EASI > 7	435 (71.9%)	

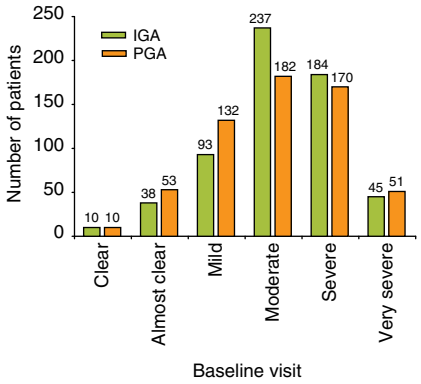

Figure 2 Global severity of AD as assessed by the physicians (IGA, n = 607) and the patients (PGA, n = 598) at baseline.

At baseline, the mean body surface area affected was 18.4% ± 21.7% with eczematous lesions primarily located on the face, flexures, neck and hands.

Subjective disease severity and symptoms of AD, quality of life and patient satisfaction

At baseline, the mean POEM score was 16.3 ± 7.5 reflecting a moderate-to-severe subjective disease severity[36] (Table 3). The mean NRS symptoms score (0–10) for the last 3 days was 5.4 ± 2.7 for pruritus, 3.4 ± 2.6 for pain and 4.3 ± 3.3 for sleep disturbance. The mean DLQI value was 11.3 ± 7.5 (out of 30 points) with almost equal percentages of patients with a DLQI below and above 10 points (i.e. at least moderately affected quality of life). The median DLQI value was 11 points. Patient satisfaction with medical care and treatment for AD was classified as 'fair' at this time point. An overview on these results is given in Table 3.

Disease activity and systemic treatment for AD before inclusion into the registry

The vast majority of patients (70.2%) reported persistent AD during the 12 months previous to the baseline visit (Table 4). Information on systemic treatment for AD before inclusion into the registry is listed in Table 5. A large proportion of the patients had received systemic glucocorticosteroids (60.9%) or cyclosporine A (36.8%) before enrolment in the registry. The percentages of patients who had received other common drugs for systemic treatment such as methotrexate (MTX), azathioprine,

Table 3 Results from POEM, subjective symptoms of AD, quality of life and patient satisfaction at baseline

Assessments	*n*	Mean ± SD
POEM (0–28) 0 (0–2 points) = clear/almost clear, 1 (3–7 points) = mild, 2 (8–16 points) = moderate, 3 (17–24 points) = severe, 4 (25–28 points) = very severe	596	16.3 ± 7.5
Patient's report on... (in the past 3 days)		
Pruritus (0–10)	598	5.4 ± 2.7
Pain (0–10)	598	3.4 ± 2.6
Sleep disorder (0–10)	598	4.3 ± 3.3
Quality of life 0 (0–1 points) = no effect at all, 1 (2–5 points) = small effect, 2 (6–10 points) = moderate effect, 3 (11–20 points) = very large effect, 4 (21–30 points) = extremely large effect		
DLQI (0–30)	588	11.3 ± 7.5
DLQI < 10	272 (46.3%)	
DLQI ≥ 10	316 (53.7%)	
Patient satisfaction with medical care for atopic dermatitis (*n* = 597) **(0 = very dissatisfied, 10 = very satisfied)**		
0- to 10-point scale ± SD		7.2 ± 2.7
Patient satisfaction with medical treatment for atopic dermatitis (*n* = 598)		
0- to 10-point scale ± SD		6.1 ± 2.9

mycophenolate mofetil/mycophenolic acid and dupilumab were below 10%. Finally, approximately 10% of patients had received less conventional systemic therapeutics for AD (as reported by the patients).

Systemic treatment at baseline

Figure 3 depicts current and prescribed systemic treatment at the baseline visit. Here, dupilumab was the leading substance documented as 'current' ($n = 74$) and 'prescribed' ($n = 192$). The second leading treatment (current and prescribed) at baseline was cyclosporine A, followed by oral glucocorticosteroids.

Discussion

The TREATgermany registry was originally initiated by the German Society of Dermatology (DDG) in 2011 as the world's first registry on adult patients severely affected by AD.[20] The registry was founded to fulfil the clear need to generate data from real-world scenarios in a prospective, longitudinal setting, combining important information from larger cross-sectional studies based, in many cases, on poorly defined clinical phenotypes. To allow comparability of AD care and enable future pooling of data for safety and effectiveness analyses across European countries, a core data set has been agreed upon between the different national AD registries in Europe.[37] TREATgermany is therefore the first of a family of European registries following a comparable design and the same set of core outcomes, thus enabling subsequent joint analysis.[37]

Table 4 Disease activity before inclusion into the registry

Month with active atopic dermatitis in the preceding year	*N*	%
0–12 months	180	29.8
12 months (continuous)	424	70.2

In this article, the concept and current status of clinical baseline data of the registry are presented. These data are considered to be representative for adults with AD in Germany as they are obtained under 'real-life' conditions of a total of 612 patients from 32 national recruiting sites.

Patients of the current TREATgermany study population are predominantly highly educated. Given the fact that a higher level of education is commonly related to a higher socio-economic status, this observation is consistent with findings of a recently published study reporting a higher prevalence of skin and atopic diseases in patients with middle or high socio-economic status compared against those with low socio-economic status.[38] In a UK child cohort, eczema was also reported to be more common in more advantaged children.[39] In fact, as more data on the socio-economic status have been published for children than for adults with AD, this registry opens new perspectives in the field of demographic data in AD. In other chronic inflammatory skin diseases, such as psoriasis, the level of education has been identified as a significant predictor for accepting additional efforts/expenses to undergo further health care.[40] Thus, findings on educational and socio-economic aspects from the TREATgermany registry can be considered as an important starting point for further investigation into AD patients' characteristics and behaviour with regard to receiving medical care.

Inhalant allergy is reported by a percentage of 44.6% (bronchial asthma) and 66.8% (allergic rhinitis) of TREATgermany registry patients, respectively. Epidemiological studies have demonstrated that inhalant allergens, namely house dust mite and pollen, are the main cause of clinically relevant allergy in

Table 5 Systemic treatment for AD before inclusion into the registry

Substance	*n* with systemic treatment	% referred to 612 registry patients
Glucocorticosteroids	373	60.9
Cyclosporine A	225	36.8
MTX	36	5.9
Azathioprine	27	4.4
Mycophenolate mofetil/mycophenolic acid	18	2.9
Dupilumab	49	8.0
Other systemic therapeutics (alphabetical order)	**53**	**8.7**
Alitretinoin	12	
Alitretinoin, omalizumab	1	
Anti-IL5	1	
Baricitinib	1	
'Biologic' or study medication (during trial)	6	
Citalopram	1	
Dapsone	1	
(IgE-) immunoadsorption	5	
Immunglobulins	1	
Isotretinoin	1	
Itraconazole	1	
Leflunomide	1	
Montelukast	1	
Nalbuphine	1	
Nemolizumab	2	
Omalizumab	5	
Omalizumab, rituximab	1	
Omega fatty acids	1	
Oral psoralene + UVA (PUVA)	1	
Placebo-controlled clinical trial with Janus kinase inhibitor	2	
Secukinumab	1	
Tralokinumab	6	

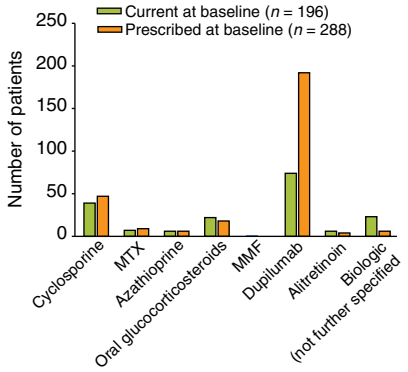

Figure 3 Current and prescribed systemic treatment in the TREATgermany baseline cohort (n = 612).

Middle and Northern Europe. Surprisingly, in the TREATgermany baseline population allergic sensitization to mould and food was most often documented. In approximately 20–23% of the patients, 'unclear' conditions regarding both of these allergens were documented. Whilst these results support studies reporting a higher rate of 'self-diagnosis' with respect to food allergy than can be confirmed by evidence-based diagnostic methods,[41] this finding demonstrated a substantial need for facilitating patient empowerment and access to specific health care for evidence-based allergy diagnosis.[42] However, for the registry, allergic sensitization was assessed by the physicians. Here, it must be critically remarked that this information may be based on the patient statement in addition to IgE results. Regarding this issue, such a lack of clarity of the TREATgermany questionnaire remains to be solved in the future.

Regarding the remaining comorbidities reported at baseline, one-fifth of the TREATgermany population was reported to suffer from arterial hypertension. Despite 36.8% of patients receiving cyclosporine A, of which arterial hypertension is a common side-effect, this rate is less than that of the general population in Germany.[43] However, further data analysis of the patient questionnaires demonstrated an elevated rate of depression when compared with the rate of self-reported depression in the adult population Germany (10% vs. 7.7%).[44] Indeed, the relevance of psychiatric comorbidities in AD is an intensively investigated subject.[45] A recently published meta-analysis revealed a significant association between AD and depression and anxiety.[11] However, the corresponding data published so far seem to be partially conflicting and are still under debate. Whilst for psoriasis patients a more comprehensive understanding of the pathogenesis finally led to the current concept of a systemic disease, this cannot be concluded for AD (with the exception of type 2-associated diseases) based on the data currently available. Finally, no increased prevalence of cardiovascular diseases was observed in the TREATgermany baseline population. Recent publications based on genome-wide and epidemiological data analysis further indicate associations between AD and other inflammatory and autoimmune diseases.[7,46] However, with regard to diabetes mellitus, chronic inflammatory bowel diseases or rheumatoid arthritis, such an association cannot be concluded from the TREATgermany baseline population data. Therefore, further studies – also on behalf of the TREATgermany database – are necessary to better elucidate the potential relevance of non-allergic comorbidities and how they are connected to AD.

With regard to one of the most feared complications in AD, namely eczema herpeticum, several efforts have been undertaken to define its epidemiology and particular pathogenesis in more detail.[47–49] In the TREATgermany baseline subpopulation, the rate of self-reported extensive herpes infection, that is eczema herpeticum, was 23.5%. This rather high

rate of herpes infection can be explained in part by the severity of AD, since the risk of severe herpes infection increases with the severity of AD.[50] Indeed, 76.7% (IGA), 85.1% (oSCORAD) and 71.9% (EASI) of patients were scored as moderate-to-severe AD.

Interestingly, patients scored disease severity significantly lower than physicians, which raises the question as to whether patients with AD might have a higher capacity to suffer with the disease or develop distinct coping mechanisms. Stigmatization is a well-known problem in AD,[51] and the body regions most commonly affected in this cohort were the face and hands. Accordingly, the mean subjective disease severity (POEM) was scored moderate and the mean QoL was reported to be very largely affected (DLQI). This is in accordance with a recent analysis of data from France, Germany, Italy, Spain and United Kingdom that revealed a significant burden on health, health-related quality of life, productivity, activities and health care reported by AD patients.[52] In the TREATgermany baseline population, the burden inflicted by pruritus was most highly scored, confirming previous publications reporting pruritus and sleeplessness as the most relevant factors for QoL in AD.[9] As expected, the TREATgermany patient's satisfaction with medical care and treatment at baseline was fair. So, we come to the conclusion that further efforts have to be made to improve medical health care for adult AD patients. Moreover, these data remain to be investigated in more depth from a psychological point of view considering the higher rate of depression in adult AD patients.

According to the AD severity defined for inclusion into the registry, a high rate of patients received systemic treatment prior to inclusion. More than half of the patients had received oral glucocorticosteroids despite the corresponding guidelines for the treatment of AD only recommending glucocorticosteroid treatment in exceptional cases of acute flares, with no recommendation for long-term treatment.[53,54] Up to January 2019, the second highest percentage had received cyclosporine A. This was in accordance with the guidelines at that time. However, regarding contraindications for cyclosporine A treatment, approximately 25% of the TREATgermany patients reported arterial hypertension or renal insufficiency, skin cancer or PUVA therapy in the past. The spectrum of other systemic immunosuppressants the patients had received also mainly followed the guideline recommendations in and before December 2018. However, the systemic drug patients were most often receiving at baseline, and which was most often prescribed at baseline, was clearly dupilumab.

In conclusion, baseline characteristics of the TREATgermany population provide an informative insight into the current healthcare situation of patients with moderate-to-severe AD in Germany. These 'real-life' data demonstrate a high burden inflicted by the disease with a relevant impact on the patients' quality of life. With regard to systemic treatment of AD, the largest proportion of TREATgermany patients was already treated with or prescribed dupilumab at baseline. However, current findings indicate the urgent need for further alternative agents in order to achieve a perceptible improvement of quality of life of patients with moderate-to-severe AD.

Future analyses of data will evaluate outcomes of patients with different treatments, reasons for discontinuation and rate of adverse events. This real-world data collection initiative in Germany will certainly provide physicians with a better understanding of their moderate-to-severe AD patients, guide therapeutic decision-making and help to improve the management of these patients.

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