ORIGINAL ARTICLE

The patient-reported disease burden in adults with atopic dermatitis: a cross-sectional study in Europe and Canada

M. de Bruin-Weller,[1] A. Gadkari,[2] S. Auziere,[3] E.L. Simpson,[4] L. Puig,[5] S. Barbarot,[6] G. Girolomoni,[7] K. Papp,[8] A.E. Pink,[9] G. Saba,[3] T. Werfel,[10] L. Eckert[11,*]

[1]University Medical Center Utrecht, Utrecht, The Netherlands
[2]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA
[3]Kantar – Health Division, Paris, France
[4]Oregon Health and Science University, Portland, OR, USA
[5]Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain
[6]Centre Hospitalier Universitaire de Nantes, Nantes, France
[7]Universita di Verona, Verona, Italy
[8]Probity Medical Research, Waterloo, ON, Canada
[9]St. John's Institute of Dermatology, Guy's and St. Thomas' NHS Foundation Trust and Kings College London, London, UK
[10]Hannover Medical University, Hannover, Germany
[11]Sanofi, Chilly-Mazarin, France
*Correspondence: L. Eckert. E-mail: Laurent.Eckert@sanofi.com

Abstract

Background Cross-sectional data on patient burden in adults with atopic dermatitis (AD) from real-world clinical practice are limited.

Objective This study compared patient-reported burden associated with adult AD across severity levels from clinical practices in Canada and Europe.

Methods This study included adults (18–65 years) diagnosed with AD by dermatologists, general practitioners or allergists. Participants categorized as mild (n = 547; 37.3%), moderate (n = 520; 35.4%) or severe (n = 400; 27.3%) based on Investigator's Global Assessment completed a questionnaire that included pruritus and pain numerical rating scales, Patient-Oriented-Scoring of Atopic Dermatitis (PO-SCORAD) itch and sleep visual analogue scales, Dermatology Life Quality Index (DLQI), and the Hospital Anxiety and Depression Scale (HADS). Participants were also stratified by inadequate efficacy/intolerance/contraindication to cyclosporine [Cyclo; n = 62 (4 mild, 18 moderate, 40 severe)] and any systemic immunomodulatory agent [IMM; n = 104 (13 mild, 31 moderate, 60 severe)] and compared with the severe group excluding participants identified as Cyclo/IMM.

Results Age was similar across severity groups; the proportion of women was higher in the mild group relative to severe (61.2% vs. 50.5%; $P < 0.001$). Compared with moderate and mild, participants with severe AD had more comorbidities, higher itch and pain severity, worse sleep and higher levels of anxiety and depression (all $P < 0.001$). Mean ± SD DLQI score among participants with severe AD (16.2 ± 6.9) showed a large effect on quality of life that was higher than those with moderate (10.2 ± 6.3) and mild (5.5 ± 4.9) (both $P < 0.001$). The burden among Cyclo and IMM subgroups was generally similar to that of participants with severe AD.

Conclusions Adults with AD reported a substantial burden across multiple domains that was significantly higher in those with severe disease. The burden among participants in the Cyclo/IMM subgroups was similar to those with severe AD.

Received: 27 March 2019; Accepted: 20 September 2019.

Conflicts of interest

S. Barbarot has received honoraria for invited talks or scientific advice; research grants from Pierre Fabre Laboratory, Fondation pour la dermatite atopique, Bioderma, Sanofi-Genzyme, Novalac, AbbVie, Novartis, Janssen and Celgene; and non-financial support from AbbVie, Novartis and Janssen. A. Gadkari is an employee of and stockholder in Regeneron Pharmaceuticals, Inc. S. Auziere and G. Saba are employees of Kantar Health Division, who received funding from Sanofi to conduct the study. M. de Bruin-Weller is a consultant for Regeneron Pharmaceuticals, Inc., Sanofi Genzyme; an advisory board member for AbbVie, Regeneron Pharmaceuticals, Inc., Sanofi Genzyme, Pfizer, UCB, Eli Lilly; and principal investigator for AbbVie, Regeneron Pharmaceuticals, Inc., Sanofi Genzyme, Pfizer. A. Pink has given talks or consulted for Sanofi, Novartis, Almirall,

Leo Pharma, Eli Lilly, AbbVie and La Roche Posay. G. Girolomoni has been principal investigator in clinical trials sponsored by and/or and has received personal fees from AbbVie, Abiogen, Almirall, Amgen, Bayer, Biogen, Celgene, Eli Lilly, Galderma, Hospira, Janssen, Leo Pharma, Merck, MSD, Mundipharma, Novartis, Pfizer, Pierre Fabre, Regeneron Pharmaceuticals, Inc., Samsung, Sandoz, Sanofi and Sun Pharma. Kim Papp reports grants and personal fees from AbbVie, Amgen, Anacor, Baxalta, Biogen, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Dermira, Dow Pharma, Galderma, Janssen, Kyowa Hakko Kirin, Leo Pharma, Merck (MSD), Merck Serono, Novartis, Pfizer, Regeneron Pharmaceuticals, Inc., Roche, Sanofi, Takeda, UCB and Valeant, and personal fees from Akros, AstraZeneca, Baxter, Cipher, Eli Lilly, Forward Pharma, Meiji Seika Pharma, Mitsubishi Pharma and Mylan. L. Puig has received consultancy honoraria from and participated in clinical trials sponsored by Regeneron Pharmaceuticals, Inc. and Sanofi. T. Werfel has received honoraria for invited talks or scientific advice and research grants from AbbVie, Allmiral, ALK Scherax, Astellas, Janssen/JNJ, Leo, Eli Lilly, Meda, Novartis, Pfizer, Regeneron Pharmaceuticals, Inc./Sanofi, Roche, Stallergen, Takeda and Ziarco. E.L. Simpson has received grant/research support from AbbVie, Eli Lilly Co., Galderma, Kyowa Hakko Kirin, Leo Pharmaceutical Co., Merck, Pfizer, Regeneron Pharmaceuticals, Inc. and a consulting fee from AbbVie Inc., Boehringer-Ingelheim, Dermavant, Eli Lilly, Forte Bio, Incyte, Leo Pharmaceutical Co., Menlo Therapeutics, Pfizer, Pierre Fabre Dermo Cosmetique, Regeneron Pharmaceuticals, Inc., Sanofi Genzyme and Valeant. L. Eckert is an employee of and stockholder in Sanofi.

Funding source

This study was funded by Regeneron Pharmaceuticals, Inc. and Sanofi.

Introduction

Atopic dermatitis (AD) is a chronic, often relapsing inflammatory skin disease with a pathology characterized by skin barrier dysfunction and immune dysregulation[1]; clinical presentation includes pruritus (itch), xerosis (abnormally dry skin) and eczematous lesions. The presence of comorbid conditions and serum biomarkers supports AD as a systemic, inflammatory disorder.[2–4]

For many patients, AD is a lifelong condition, and for all patients, it is associated with substantial effects on their daily lives. These effects, which appear to increase with greater AD severity, include persistent itch, sleep disturbances, impaired mental health, reductions in function, productivity and health-related quality of life (HRQoL), and an impact on life decisions.[5–9] Despite characterization of the multidimensional burden, cross-sectional data on the patient-reported burden in adults with AD from real-world clinical practice are limited.

Given the need for real-world data, this study compared the patient-reported burden associated with adult AD across severity levels from clinical practices in Canada and Europe. The burden was also characterized in a subpopulation of participants in whom cyclosporine and other systemic IMM agents do not represent adequate therapeutic options.

Methods

Study design and populations

This was an international, cross-sectional, observational study of adults with AD seen by investigators in routine clinical practice in Canada, France, Germany, Italy, Spain and the United Kingdom. Investigators were eligible if they personally initiate medical treatment for adult patients with AD and managed and treated a minimum number of these patients over the past month (≥10 for dermatologists, of which a minimum of 3 were moderate or severe, and ≥5 for general practitioners and allergists). Patient participants were required to provide written informed consent prior to participation. The study was approved at country level by the appropriate ethics committees.

The study population consisted of adults (18–65 years, inclusive) diagnosed with AD by dermatologists (all countries), general practitioners (France and the United Kingdom) or allergists (France). Participants were excluded if they participated in any randomized controlled trial for treatment of AD within the past 12 months. Participants were stratified by AD severity as mild, moderate or severe based on the Investigator's Global Assessment (IGA). Investigators were requested to evenly include patients across severity levels during enrolment to enable sufficient sample sizes, as severe AD has the lowest prevalence among severity levels regardless of method of severity assessment.[10] To further characterize the burden among those who may be considered more difficult to treat in a real-world clinical setting, participants were additionally stratified based on investigator opinion of whether they previously demonstrated inadequate efficacy for or had contraindications or intolerance to systemic immunomodulatory agents (subpopulation abbreviated as IMM, which included methotrexate, azathioprine, cyclosporine and mycophenolate mofetil). This stratification was regardless of their AD severity, that is using a population-level approach. As

Table 1 Demographic and clinical characteristics

Variable	Value			
Total population	**Mild**	**Moderate**		**Severe**
Number of participants (%)	547 (37.3)	520 (35.4)		400 (27.3)
Women, *n* (%)	335 (61.2)*	274 (52.7)		202 (50.5)
Age, years, mean (SD)	38.2 (13.2)	38.0 (12.8)		38.4 (12.8)
Age at diagnosis, *n* (%)				
<2 years	66 (12.1)*	85 (16.3)†		86 (21.5)
2–4 years	49 (9.0)†	58 (11.2)		58 (14.5)
5–8 years	52 (9.5)†	40 (7.7)		24 (6.0)
9–12 years	38 (6.9)	34 (6.5)		24 (6.0)
13–18 years	44 (8.0)	40 (7.7)		30 (7.5)
>18 years	290 (53.0)*	252 (48.5)†		166 (41.5)
Missing	8 (1.5)	11 (2.1)		12 (3.0)
SCORAD score, mean (SD)	29.2 (14.6)*	49.2 (16.0)*		68.4 (14.9)
EASI score, mean (SD)	2.6 (3.6)*	9.5 (8.0)*		22.7 (13.9)
Variable	**Value**			
Subpopulations	**Cyclo (*n* = 62)**	**Severe excluding Cyclo (*n* = 360)**	**IMM (*n* = 104)**	**Severe excluding IMM (*n* = 340)**
Women, *n* (%)	23 (37.1)‡	187 (51.9)	43 (41.3)	175 (51.5)
Age, years, mean (SD)	40.6 (12.6)	38.1 (12.7)	40.6 (13.4)	38.0 (12.6)
Age at diagnosis, *n* (%)				
<2 years	21 (33.9)	73 (20.3)	35 (33.7)‡	65 (19.1)
2–4 years	13 (21.0)	49 (13.6)	22 (21.2)‡	44 (12.9)
5–8 years	3 (4.8)	23 (6.4)	5 (4.8)	22 (6.5)
9–12 years	3 (4.8)	21 (5.8)	6 (5.8)	21 (6.2)
13–18 years	0	30 (8.3)	1 (1.0)‡	29 (8.5)
>18 years	21 (33.9)	153 (42.5)	34 (32.7)	148 (43.5)
SCORAD score, mean (SD)	60.1 (17.2)§	68.7 (15.0)	60.6 (17.1)§	68.7 (14.9)
EASI score, mean (SD)	19.4 (13.4)	22.5 (14.0)	18.0 (13.2)‡	22.5 (14.0)

*$P < 0.001$ and †$P \leq 0.05$ vs. IGA severe; ‡$P < 0.05$ and §$P < 0.001$ for Cyclo or IMM groups vs. severe groups excluding Cyclo/IMM participants, respectively.

Cyclo, participants with inadequate efficacy for or contraindications or intolerance to cyclosporine; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; IMM, participants with inadequate efficacy for or contraindications or intolerance to any systemic immunomodulatory agent (including Cyclo participants); SCORAD, Scoring of Atopic Dermatitis; SD, standard deviation.

cyclosporine is the only approved systemic immunomodulatory therapy, a separate subpopulation was created consisting only of study participants who had previously demonstrated inadequate efficacy for or had contraindications or intolerance to cyclosporine (subpopulation abbreviated Cyclo). Neither participants who had refused any systemic treatment nor those who were treated with systemic corticosteroids were included in these subpopulations, as systemic corticosteroids are not recommended for chronic administration.[11]

Outcomes

The presence of atopic and non-atopic comorbidities was abstracted from the medical records of the study participants by the investigator. Two clinical measures were included, the Eczema Area and Severity Index (EASI)[12] and the Scoring of Atopic Dermatitis (SCORAD) scale.[13] Participants completed a pen-and-paper questionnaire that consisted of translations in their native language of validated measures and stand-alone questions that assessed diverse domains affected by AD. The Pruritus Numerical Rating Scale (NRS; 0 = no itch to 10 = worst itch imaginable)[14] measured average overall itch within the past 24 h and the Patient-Oriented SCORAD (PO-SCORAD) visual analogue scale (VAS; 0 = no itching, 10 = unbearable itching)[15] assessed itch intensity over the past 3 days. Worst pain within the past 24 h was evaluated using a pain NRS (0 = no pain, 10 = worst imaginable pain). Sleep quantity and quality were assessed using the PO-SCORAD sleep VAS (0 = no trouble sleeping to 10 = unable to sleep over the past 3 days).[15] As stand-alone questions, item 2 from the Patient-Oriented Eczema Measure (POEM) was used to determine the frequency of sleep disturbances over the past week,[16] and question 4 modified from the Pittsburgh Sleep

Quality Index[17] was used to determine the number of hours of sleep per night over the past week.

The Hospital Anxiety and Depression Scale (HADS)[18] evaluated mental health based on two subscales with score ranges of 0–21 that determine the extent of anxiety and depression; scores ≥8 indicate the presence of anxiety or depression symptoms and scores ≥11 are suggestive of clinical anxiety or depression. The Dermatology Life Quality Index (DLQI)[19] assessed the impact of AD on HRQoL over the past week (score range 0–30, higher scores indicate greater impact). Stand-alone questions assessed productivity as days missed from work or study during the past 4 weeks.

Statistical analysis

Outcomes were compared between participants with IGA-rated severe AD and those with mild and moderate disease. Additionally, the IMM and Cyclo groups, regardless of IGA severity, were compared with IGA severe after excluding the patients who were IGA severe and part of the IMM and Cyclo groups, respectively; that is all statistical comparisons are made between groups that did not have overlapping populations. To explore the robustness of this comparison, a post hoc sensitivity analysis was conducted for the IMM subpopulation with severe AD vs. the IGA group excluding these IMM patients. Comparisons were conducted using bivariate analyses with Z-tests for categorical variables and paired-sample t-tests for continuous variables; comparisons were based on observed values. Analyses were conducted using DAISIE version 2.4.25 (ADN, Paris, France); nominal *P*-values are reported as there was no correction for multiple comparisons.

Results

Demographic and clinical characteristics

The study population consisted of 1467 adults with AD (Canada, $n = 127$; France, $n = 288$; Germany, $n = 287$; Italy, $n = 288$; Spain, $n = 290$; and the United Kingdom, $n = 187$) who were enroled by 245 clinicians. The stratification criteria resulted in similar proportions of participants across severity levels (mild, 37.3%; moderate, 35.4% and severe, 27.3%; Table 1). While the Cyclo and IMM subpopulations consisted of participants from all severity levels, the majority of these participants had severe AD, 64.5% and 57.7%, respectively (Fig. 1a). Inadequate response was the most frequent categorization of Cyclo (50.0%) and IMM (58.7%) participants (Fig. 1b).

In the total population, severe AD comprised a significantly lower proportion of women relative to mild (50.5% vs. 61.2%; $P < 0.001$; Table 1), and age was similar across severity levels. However, the proportion of participants with severe AD who were diagnosed <2 years old, 21.5%, was higher relative to those with mild (12.1%; $P < 0.001$) and moderate AD, (16.3%; $P < 0.05$), and conversely, lower proportions of participants with severe AD were diagnosed as adults (Table 1).

Eczema Area and Severity Index and SCORAD scores increased with greater AD severity; participants with severe disease had significantly higher scores than those with mild and moderate AD (all $P < 0.001$; Table 1).

In the subpopulations compared with those who had severe AD, the Cyclo group had a lower proportion of women (37.1% vs. 51.9%; $P < 0.05$), and higher proportions of IMM participants were diagnosed at earlier ages (Table 1). The scores on EASI and SCORAD were significantly higher among participants

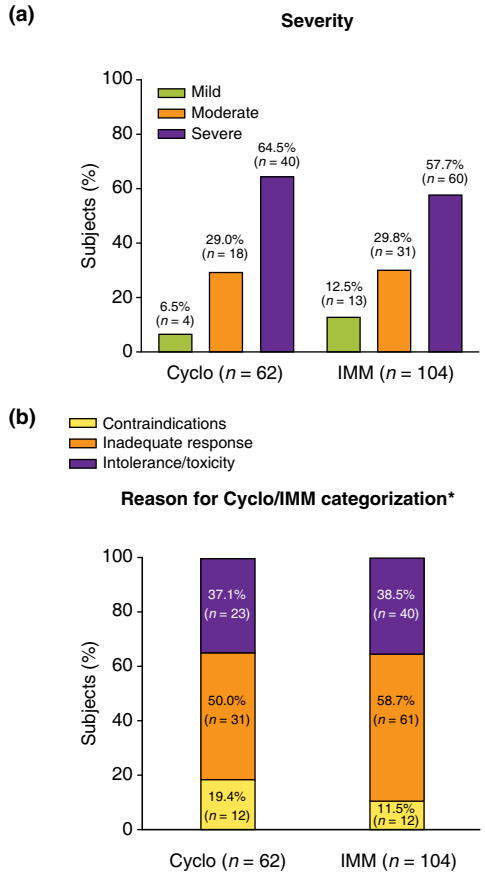

Figure 1 Investigator Global Assessment-rated severity (a) and reasons for categorization (b) of the Cyclo and immunomodulatory agent (IMM) subpopulations. *Numbers of patients for each reason add up to more than the group number, as some patients were characterized by multiple reasons. Cyclo, participants with inadequate efficacy for or contraindications or intolerance to cyclosporine; IMM, participants with inadequate efficacy for or contraindications or intolerance to any systemic immunomodulatory agent (including Cyclo participants).

with severe AD relative to the Cyclo and IMM subgroups (Table 1).

The number of atopic comorbidities increased with AD severity and was significantly higher for asthma, food allergies and atopic keratoconjunctivitis among participants with severe disease compared with those who had mild and moderate AD (Table 2). The proportion of participants with ≥1 comorbid non-atopic condition was higher among those with severe AD (54.3%) relative to mild (41.7%; $P < 0.001$) and moderate (46.7%; $P < 0.05$; Table 2); comorbid emotional or mental conditions had the highest prevalence across severity levels and showed significance ($P < 0.001$) for those with severe relative to mild and moderate AD.

The proportions of Cyclo and IMM participants with ≥1 atopic comorbidity were similar to their respective severe comparator groups (Table 2). Only for the individual atopic comorbidity of asthma was there a significantly higher prevalence relative to severe for Cyclo (61.3% vs. 41.4%; $P < 0.05$) and IMM (59.6% vs. 40.3%; $P < 0.001$). Relative to severe, significantly higher proportions of the Cyclo (77.4% vs. 51.7%; $P < 0.001$) and IMM (76.0% vs. 50.3%; $P < 0.001$) subgroups had ≥1 non-atopic comorbidities, with significantly higher proportions relative to severe for emotional/mental, cardiac/vascular and urology/renal conditions (Table 2).

Patient-reported burden in total population

Patient-reported scores on measures of itch and pain were consistently worse with increasing AD severity, and participants with severe AD reported significantly higher scores, indicating more severe itch and pain, relative to those with mild and moderate AD (all $P < 0.001$; Fig. 2). Greater effects on sleep quantity and quality were reported by participants with severe AD relative to those with moderate and mild disease ($P < 0.001$; Fig. 3).

Participants with severe AD reported significantly higher anxiety and depression than those with moderate and mild AD (both $P < 0.001$; Table 3), with anxiety consistently higher than

Table 2 Selected comorbid conditions

Variable	Number (%) of participants			
Total population	**Mild (*n* = 547)**	**Moderate (*n* = 520)**	**Severe (*n* = 400)**	
≥1 atopic comorbidity	322 (58.9)*	388 (74.6)†	322 (80.5)	
Asthma	111 (20.3)*	165 (31.7)*	174 (43.5)	
Food allergies	55 (10.1)*	98 (18.8)†	101 (25.3)	
Seasonal allergies	179 (32.7)*	219 (42.1)	176 (44.0)	
Atopic keratoconjunctivitis	2 (0.4)*	5 (1.0)†	12 (3.0)	
≥1 non-atopic comorbidity	228 (41.7)*	243 (46.7)†	217 (54.3)	
Emotional or mental conditions	92 (16.8)*	107 (20.6)*	125 (31.3)	
Cardiac/vascular conditions	46 (8.4)	56 (10.8)	48 (12.0)	
Musculoskeletal/integument conditions	34 (6.2)	37 (7.1)	35 (8.8)	
Endocrine/metabolic conditions	41 (7.5)	52 (10.0)	44 (11.0)	
Urology/renal condition	10 (1.8)	14 (2.7)	9 (2.3)	
Variable	**Number (%) of participants**			
Subpopulations	**Cyclo (*n* = 62)**	**Severe excluding Cyclo (*n* = 360)**	**IMM (*n* = 104)**	**Severe excluding IMM (*n* = 340)**
≥1 atopic comorbidity	53 (85.5)	289 (80.3)	85 (81.7)	272 (80.0)
Asthma	38 (61.3)‡	149 (41.4)	62 (59.6)§	137 (40.3)
Food allergies	20 (32.3)	86 (23.9)	31 (29.8)	81 (23.8)
Seasonal allergies	32 (51.6)	156 (43.3)	45 (43.3)	151 (44.4)
Atopic keratoconjunctivitis	2 (3.2)	10 (2.8)	4 (3.8)	8 (2.4)
≥1 non-atopic comorbidity	48 (77.4)§	186 (51.7)	79 (76.0)§	171 (50.3)
Emotional or mental conditions	29 (46.8)‡	102 (28.3)	45 (43.3)‡	94 (27.6)
Cardiac/vascular conditions	14 (22.6)‡	37 (10.3)	24 (23.1)§	32 (9.4)
Musculoskeletal/integument conditions	6 (9.7)	31 (8.6)	14 (13.5)	28 (8.2)
Endocrine/metabolic conditions	7 (11.3)	38 (10.6)	13 (12.5)	35 (10.3)
Urology/renal condition	5 (8.1)§	5 (1.4)	6 (5.8)‡	5 (1.5)

*$P < 0.001$ and †$P \leq 0.05$ vs. IGA severe; ‡$P \leq 0.05$ and §$P \leq 0.001$ for Cyclo or IMM groups vs. severe groups excluding Cyclo/IMM participants, respectively.

Cyclo, participants with inadequate efficacy for or contraindications or intolerance to cyclosporine; IGA, Investigator's Global Assessment; IMM, participants with inadequate efficacy for or contraindications or intolerance to any systemic immunomodulatory agent (including Cyclo participants).

depression. Among participants with severe AD, 65.8% and 56.2% had subscale scores indicative of anxiety and depression symptoms, respectively (scores ≥8) and 40.3% and 29.9% had scores suggestive of clinical anxiety and depression (scores ≥11), respectively; these proportions were higher than the respective proportions of participants who had mild and moderate AD (all $P < 0.001$; Table 3).

The mean DLQI score among participants with severe AD, 16.2 ± 6.9, was higher than those with mild (5.5 ± 4.9) and moderate, 10.2 ± 6.3, respectively (both $P < 0.001$; Table 3). All individual domain scores of the DLQI increased with AD severity, and those with severe disease reported higher scores than those having moderate and mild AD (all $P < 0.001$).

Participants with severe AD who were either students or employed at least part time reported greater loss of productivity ($P < 0.05$) compared with those who had mild and moderate AD (Table 3).

Patient-reported burden in Cyclo and IMM subpopulations

The Cyclo and IMM subpopulations reported similar burdens across all outcomes relative to their severe comparator groups (Table 4), except for a lower mean score on the pruritus NRS in the IMM subpopulation relative to those with severe AD (7.0 vs. 6.5; $P < 0.05$).

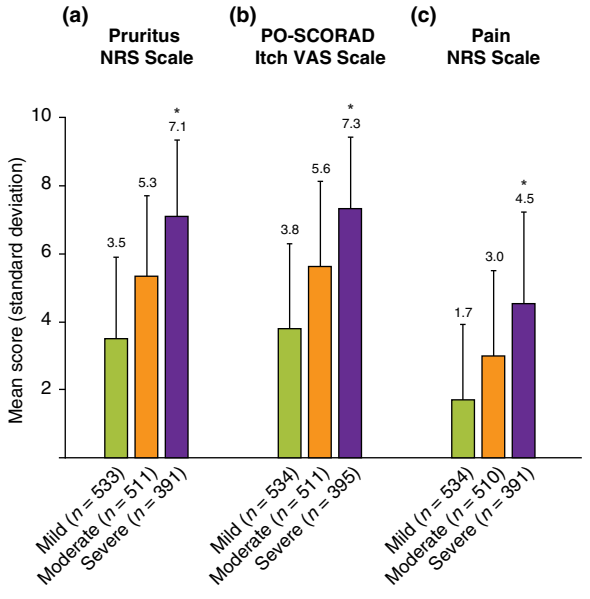

Figure 2 Impact of atopic dermatitis on patient-reported itch and pain. *$P < 0.001$ vs. mild and moderate. NRS, numerical rating scale; PO-SCORAD, Patient-Oriented Scoring of Atopic Dermatitis scale; VAS, visual analogue scale.

Results of the sensitivity were generally similar to that of the main analysis, with a burden that was comparable between the severe IMM subpopulation and the severe group excluding those in the IMM subpopulation (Table 5). The only exceptions were slightly, but statistically significant ($P < 0.05$) higher pain NRS scores and greater anxiety among the IMM severe subpopulation.

Discussion

This study continues the real-world characterization of the adult burden of AD by complementing a previous study in the United States that described the high burden associated with moderate/severe AD and showed that inadequate disease control was common and exacerbated the disease burden.[20] The current analysis

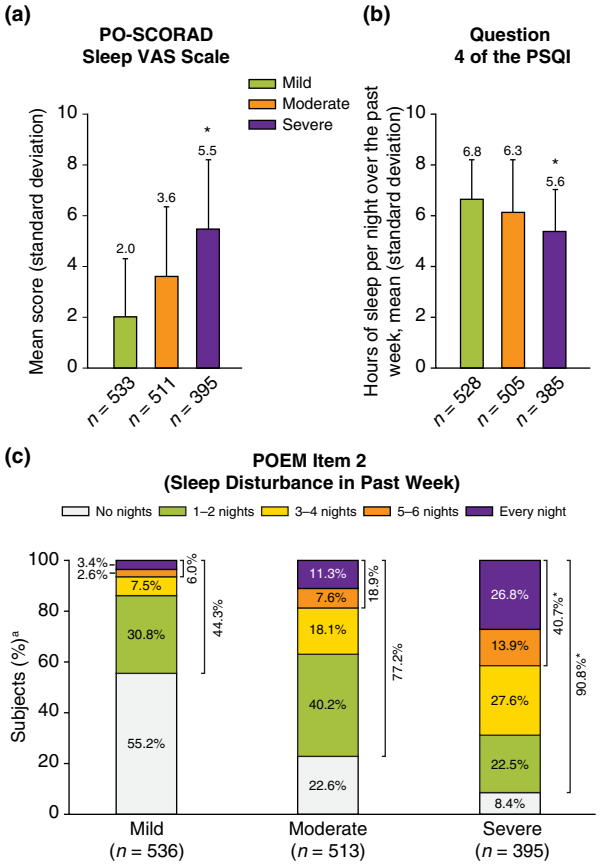

Figure 3 Impact of atopic dermatitis on patient-reported sleep problems. *$P < 0.001$ vs. mild and moderate. [a]Percentages sum to <100% as data were missing from seven subjects (three mild, one moderate and three severe). POEM, Patient-Oriented Eczema Measure; PO-SCORAD, Patient-Oriented Scoring of Atopic Dermatitis scale; PSQI, Pittsburgh Sleep Quality Index; VAS, visual analogue scale.

expands on those results by presenting data from Canada and the EU that represent a community-based (office and hospital practices) population rather than academic medical centres as in the U.S. study.

The proportion of women was highest among the mild AD severity group and was statistically significant compared with severe. Although the clinical relevance of this observation is unclear, it is possible that women may make clinical visits more frequently than men even when their AD is mild, as women engage in healthcare-seeking behaviour more frequently than men.[21,22] Almost half of the participants (48.3%) reported being diagnosed after 18 years of age, consistent with other studies in which 37–59% of individuals reported diagnosis during adulthood.[6,20] However, diagnosis does not necessarily equate with onset, and the time of AD onset remains unknown. Adult-onset AD has been suggested to represent, at least in some cases, individuals who may have forgotten their childhood disease,[23] most likely a result of recall bias, as participants with more severe childhood AD may remember their disease better than those with less severe childhood AD. Despite the uncertainty regarding onset, the proportion of participants who reported being diagnosed <2 years old increased with severity, providing support for the concept that earlier onset may be associated with persistent and more severe disease in adulthood.[24,25]

The comorbidity burden, which increased with AD severity, was consistent with the recognized association between AD and other atopic conditions, including those that are considered components of the atopic march.[1,26,27] Among the non-atopic comorbidities, emotional or mental conditions had the highest prevalence regardless of severity, followed by cardiovascular comorbidities. The presence of the former is not surprising, given that a substantial proportion of participants reported HADS scores that are considered indicative of clinical anxiety and depression. The burden of cardiac and vascular conditions is consistent with Silverberg *et al.*[28] and further supports an association between cardiovascular disease and AD severity.

The patient-reported burden also appeared to increase with greater disease severity and was significantly higher for those with severe AD vs. both mild and moderate disease across all outcomes. This association between AD severity and burden was generally consistent with the U.S. study,[20] and the current stratification across 3 severity levels rather than combined moderate/severe enabled a more granular assessment, albeit statistical comparison of mild with moderate was not performed.

Within each AD severity level, itch intensity scores were similar on the NRS and SCORAD VAS despite the fact that the recall periods are 24 h for the former and 3 days for the latter, suggesting that itch intensity is generally maintained over at least short periods of time and likely correlates with AD severity. Given that

Table 3 Impact of atopic dermatitis severity on patient-reported mental health, health-related quality of life and productivity

Outcome	Mild	Moderate	Severe
HADS, *n*	536	513	395
Total score, mean (SD)	9.2 (7.0)*	12.8 (7.4)*	17.6 (7.9)‡
HADS-A score, mean (SD)	5.5 (4.0)*	7.3 (4.2)*	9.4 (4.1)‡
HADS-D score, mean (SD)	3.8 (3.7)*	5.5 (3.9)*	8.2 (4.4)‡
HADS-A ≥8, *n* (%)	135 (25.2)*	228 (44.4)*	260 (65.8)
HADS-A ≥11, *n* (%)	59 (11.0)*	118 (23.0)*	159 (40.3)
HADS-D ≥8, *n* (%)	92 (17.2)*	157 (30.6)*	222 (56.2)
HADS-D ≥11, *n* (%)	33 (6.2)*	60 (11.7)*	118 (29.9)
DLQI, *n*	533	511	387
Total score, mean (SD)	5.5 (4.9)*	10.2 (6.3)*	16.2 (6.9)
Symptoms and feelings, mean (SD)	2.0 (1.3)*	3.1 (1.5)*	4.3 (1.3)
Daily activities, mean (SD)	1.1 (1.3)*	2.2 (1.6)*	3.4 (1.7)
Leisure, mean (SD)	0.9 (1.4)*	1.8 (1.6)*	3.1 (1.9)
Work and school, mean (SD)	0.4 (0.8)*	1.0 (1.1)*	1.5 (1.2)
Personal relationships, mean (SD)	0.6 (1.0)*	1.3 (1.5)*	2.5 (1.9)
Treatment, mean (SD)	0.5 (0.7)*	0.9 (0.8)*	1.4 (0.9)
Productivity in past 4 weeks among part-/full-time employees or students, *n*	466	445	321
At least 1 day missed, *n* (%)	155 (33.3)*	233 (52.4)†	202 (62.9)
Total number of days missed related to atopic dermatitis, mean (SD)	0.9 ± 2.6*	2.0 ± 4.1*,§	3.7 ± 5.9¶

*$P < 0.001$ and †$P \leq 0.05$ vs. IGA severe.
‡$n = 394$. §$n = 439$; 6 participants who indicated a total number of days exceeding 4 weeks were excluded. ¶$n = 307$; 14 participants who indicated a total number of days exceeding 4 weeks were excluded.
DLQI, Dermatology Quality of Life Index; HADS, Hospital Anxiety and Depression Scale; HADS-A, HADS anxiety subscale; HADS-D, HADS depression subscale; SD, standard deviation.

Table 4 Patient-reported burden in the Cyclo and IMM populations

Outcome	Cyclo	Severe excluding Cyclo	IMM	Severe excluding IMM
Itch, *n*	62	355	102	336
NRS, mean (SD)	6.6 (2.2)	7.0 (2.2)	6.5 (2.3)*	7.0 (2.2)
PO-SCORAD VAS, mean (SD)	7.0 (2.2)	7.2 (2.1)	6.9 (2.3)	7.2 (2.1)
Pain NRS, mean (SD)	4.6 (2.5)	4.5 (2.7)	4.7 (2.7)	4.4 (2.7)
Sleep				
PO-SCORAD VAS, mean (SD) [*n*]	5.0 (2.9) [62]	5.5 (2.8) [355]	4.9 (2.9) [102]	5.5 (2.8) [336]
Sleep disturbed every night over past week (POEM item 2), *n* (%)	15 (24.2)	94 (26.5)	25 (24.5)	88 (26.2)
Sleep disturbance frequency (POEM item 2), *n* (%)				
No nights	6 (9.7)	32 (9.0)	10 (9.8)	30 (8.9)
1–2 nights	10 (16.1)	83 (23.4)	25 (24.5)	79 (23.5)
3–4 nights	20 (32.3)	95 (26.8)	28 (27.5)	89 (26.5)
5–6 nights	10 (16.1)	49 (13.8)	12 (11.8)	48 (14.3)
Every night	15 (24.2)	94 (26.5)	25 (24.5)	88 (26.2)
Hours of sleep per night over the past week, mean (SD) [*n*]	6.0 (1.5) [60]	5.6 (1.6) [347]	5.9 (1.4) [99]	5.6 (1.6) [328]
HADS, *n*	62	355	102	336
Total score, mean (SD)	17.0 (8.1)†	17.5 (7.8)	16.6 (8.1)‡	17.3 (7.8)
HADS-A score, mean (SD)	9.2 (4.2)†	9.3 (4.1)	9.1 (4.2)‡	9.3 (4.1)
HADS-D score, mean (SD)	7.8 (4.6)†	8.1 (4.3)	7.5 (4.6)‡	8.1 (4.3)
HADS-A ≥8, *n* (%)	41 (66.1)	229 (64.5)	67 (65.7)	214 (63.7)
HADS-A ≥11, *n* (%)	21 (33.9)	140 (39.4)	35 (34.3)	132 (39.3)
HADS-D ≥8, *n* (%)	31 (50.0)	199 (56.1)	51 (50.0)	187 (55.7)
HADS-D ≥11, *n* (%)	18 (29.0)	104 (29.3)	29 (28.4)	95 (28.3)
DLQI, *n*	59	350	98	331
Total score, mean (SD)	15.2 (6.8)	16.0 (6.9)	14.9 (6.9)	16.0 (6.9)
Symptoms and feelings, mean (SD)	4.0 (1.4)	4.3 (1.3)	4.0 (1.5)	4.2 (1.3)
Daily activities, mean (SD)	3.2 (1.7)	3.4 (1.6)	3.1 (1.7)	3.4 (1.7)
Leisure, mean (SD)	2.9 (1.8)	3.1 (1.9)	2.7 (1.9)	3.1 (1.9)
Work and school, mean (SD)	1.5 (1.2)	1.5 (1.2)	1.4 (1.2)	1.5 (1.2)
Personal relationships, mean (SD)	2.2 (1.7)	2.4 (1.9)	2.2 (1.8)	2.4 (1.9)
Treatment, mean (SD)	1.5 (0.8)	1.4 (1.0)	1.5 (0.9)	1.4 (0.9)
Productivity in past 4 weeks among part-/full-time employees or students, *n*	47	294	75	282
At least 1 day missed, *n* (%)	34 (72.3)	183 (62.2)	51 (68.0)	175 (62.1)
Total number of days missed related to atopic dermatitis, mean (SD) [*n*]	3.8 (5.8) [44]	3.7 (5.8) [283]	3.2 (4.9) [71]	3.7 (5.9) [271]

*$P < 0.05$ vs. for IMM vs. severe group excluding IMM participants.
†$n = 61$. ‡$n = 101$.
DLQI, Dermatology Quality of Life Index; HADS, Hospital Anxiety and Depression Scale; HADS-A, HADS anxiety subscale; HADS-D, HADS depression subscale; NRS, numerical rating scale; POEM, Patient-Oriented Eczema Measure; PO-SCORAD, Patient-Oriented Scoring of Atopic Dermatitis; SD, standard deviation; VAS, visual analogue scale.

itch is a cardinal symptom of AD and is the primary patient complaint, it was not surprising that itch was significantly greater among those with severe AD relative to mild and moderate disease. Pain severity also appeared to increase with AD severity, and this relationship expands the recognition of pain as having a tangible and measurable presence in AD that is also related to disease severity. This relationship may be especially relevant as pain and itch appear to have overlapping mechanisms,[29] and pain has previously been suggested to be, after itch, the most important item rated by patients for judging treatment response.[30] While lack of knowledge of the presence and impact of pain in AD has been identified as an important gap in the clinical presentation of AD,[31] a recent study has emphasized the contribution of pain to the burden of AD and suggested that pain correlates with other clinical and patient-reported outcomes.[32]

Reductions in quality and quantity of sleep are consistent with the observed relationship between itch and sleep[33,34] and the

Table 5 Sensitivity analysis comparing patient-reported burden in the severe IMM population compared with the severe population excluding the IMM participants

Outcome	Severe with IMM	Severe excluding IMM
Itch, *n*	59	336
NRS, mean (SD) [*n*]	7.2 (2.1) [58]	7.0 (2.2) [333]
PO-SCORAD VAS, mean (SD)	7.5 (1.9)	7.2 (2.1)
Pain NRS, mean (SD) [*n*]	5.3 (2.7) [58]*	4.4 (2.7) [334]
Sleep, *n*	59	336
PO-SCORAD VAS, mean (SD)	5.8 (2.9)	5.5 (2.8)
Sleep disturbed every night over past week (POEM item 2), *n* (%)	18 (30.5)	88 (26.2)
Sleep disturbance frequency (POEM item 2), *n* (%)		
No nights	3 (5.1)	30 (8.9)
1–2 nights	10 (16.9)	79 (23.5)
3–4 nights	20 (33.9)	89 (26.5)
5–6 nights	7 (11.9)	48 (14.3)
Every night	18 (30.5)	88 (26.2)
Hours of sleep per night over the past week, mean (SD) [*n*]	5.8 (1.4) [57]	5.6 (1.6) [328]
HADS, *n*	59	336
Total score, mean (SD) [*n*]	19.4 (8.1) [58]	17.3 (7.8) [336]
HADS-A score, mean (SD) [*n*]	10.4 (4.3) [58]*	9.3 (4.1) [336]
HADS-D score, mean (SD) [*n*]	9.0 (4.6) [58]	8.1 (4.3) [336]
HADS-A ≥8, *n* (%)	46 (78.0)*	214 (63.7)
HADS-A ≥11, *n* (%)	27 (45.8)	132 (39.3)
HADS-D ≥8, *n* (%)	35 (59.3)	187 (55.7)
HADS-D ≥11, *n* (%)	23 (39.0)	95 (28.3)
DLQI, *n*	56	331
Total score, mean (SD)	17.5 (6.8)	16.0 (6.9)
Symptoms and feelings, mean (SD)	4.6 (1.3)	4.2 (1.3)
Daily activities, mean (SD)	3.6 (1.7)	3.4 (1.7)
Leisure, mean (SD)	3.2 (1.9)	3.1 (1.9)
Work and school, mean (SD)	1.6 (1.2)	1.5 (1.2)
Personal relationships, mean (SD)	2.8 (1.8)	2.4 (1.9)
Treatment, mean (SD)	1.6 (0.9)	1.4 (0.9)
Productivity in past 4 weeks among part-/full-time employees or students, *n*	39	282
At least 1 day missed, *n* (%)	27 (69.2)	175 (62.1)
Total number of days missed related to atopic dermatitis, mean (SD) [*n*]	3.8 (5.4) [36]	3.7 (5.9) [271]

*$P \leq 0.05$ vs. for severe IMM vs. severe group excluding IMM participants.
DLQI, Dermatology Quality of Life Index; HADS, Hospital Anxiety and Depression Scale; HADS-A, HADS anxiety subscale; HADS-D, HADS depression subscale; NRS, numerical rating scale; POEM, Patient-Oriented Eczema Measure; PO-SCORAD, Patient-Oriented Scoring of Atopic Dermatitis; SD, standard deviation; VAS, visual analogue scale.

contribution of sleep disturbance to poorer health, reduced work productivity and increased healthcare resource use.[35] While results of previous studies have been inconsistent with regard to the relationship between sleep disturbance and AD severity,[36] the decremental effects on quality and quantity of sleep with increasing AD severity shown in the current analysis support such a relationship.

HADS scores showed a substantial presence of anxiety and depression symptoms, even among participants with mild and moderate AD, and also suggested the presence of clinical anxiety and/or depression. As reported in other studies, anxiety was more common than depression.[6,7,20] The proportions of participants with moderate and severe AD who had scores indicative of clinical anxiety and/or depression were lower than the proportions who had emotional or mental comorbidities recorded in their clinical history, suggesting that at least in some of these participants, these conditions may not be recognized. These results emphasize the need for mental health assessment and support as part of AD management, as meta-analyses consistently have shown an increased risk of depression and suicidality.[37–39]

The DLQI indicates the extent of effects on participants' daily lives; symptoms/feelings followed by daily activities were the domains most affected across severity levels. Higher AD severity resulted in a greater impact as indicated by higher scores on the total DLQI as well as on individual domains. The total score among those with severe AD (16.2) was consistent with a very large impact of AD on HRQoL, and the score among participants with moderate AD (10.2) was borderline between what is considered moderate (6–10) and large effects (11–20).[40] These effects on participants' daily lives were also reflected by lost productivity among those who were employed at least part time. Even among participants with mild AD, approximately one-third reported missing at least 1 day of work due to AD in the

past 4 weeks, increasing to half and almost two-thirds of participants with moderate and severe AD, respectively, with up to 3.7 missed days of work among the participants with severe disease. While previous studies have also documented substantial work and activity impairment associated with AD and their economic implications,[41–44] costs were not estimated in the current study, and only absenteeism was evaluated; presenteeism has been reported to be the primary driver of lost productivity in AD.[42,44]

The Cyclo and IMM subpopulations consisted of participants across all AD severity levels, reflecting clinically relevant groups that may be expected to encompass a range of disease severity. Notably, despite mild/moderate AD in 35% and 42% of the Cyclo and IMM populations, respectively, the patient-reported burden in these subpopulations was similar to those with severe AD after excluding those participants identified as Cyclo and IMM, respectively. The observation that inadequate efficacy and intolerance were the primary reasons for categorization of these participants emphasizes the lack of effective options for AD control, regardless of severity. Although there was no difference in mean age, significantly higher proportions of these subpopulations were diagnosed at an earlier age, possibly denoting that longer disease duration may be associated with a higher likelihood of receiving and failing immunosuppressant therapy. The results of the post hoc sensitivity analysis, with two exceptions, were comparable to the main analysis in showing similar burdens between the severe IMM subpopulation and the severe group excluding the IMM participants. Of the two exceptions, the higher anxiety is not surprising given the challenges in treating patients with severe AD who may not be amenable to use of IMM agents. While slightly higher pain severity was also reported by the severe IMM group, the pain severity remained in the moderate range in both groups. These results suggest overall robustness of the analysis and support the clinical rationale for including all severity levels in the main comparison.

Limitations

Strengths of this study were its use of international, community-based practices, with a high number of participants; many burden studies are national in scope and reflect participants evaluated from tertiary care centres. Limitations include selection bias and recall bias, and these biases should be considered when interpreting or extrapolating the results to other AD populations. In particular, the request for clinicians to evenly include participants across AD severity levels rather than sequentially may have additionally contributed to selection bias. Another limitation, also noted above, is that no comparisons were performed for mild vs. moderate participants. In this regard, while AD severity was based on IGA, other measures for categorizing AD severity may have yielded different results, as severity is a function of the measure used[45,46]; there is no measure of AD severity that is uniformly used in clinical practice, and thus evaluation of severity in the clinical setting remains challenging.[47,48] Sleep and productivity were evaluated using stand-alone questions, and their lack of validation may represent another limitation. Last, data from all countries were evaluated together, and while the survey questionnaire with all measures was administered in the language appropriate for each country, it is possible that there may be country-specific or cultural differences in the interpretation of questions and/or perceptions of AD and its impact.

In conclusion, this study from real-world clinical practice confirmed the substantial multidimensional burden reported by adults with AD includes disease-related symptoms (itch), pain, sleep disturbance, mental health and HRQoL. Participants with severe AD reported the highest burden, which was significant relative to those with less severe disease. Participants for whom cyclosporine or other systemic immunomodulators do not represent a therapeutic option had a disease burden similar to those with severe disease. These results highlight the need for additional and more effective therapeutic options. Furthermore, the high patient-reported burden associated with AD demonstrates the need for AD assessment that goes beyond clinical measures of disease activity and takes into account the patient perspective.

Acknowledgements

Medical writing support was provided by E. Jay Bienen, PhD, and funded by Sanofi and Regeneron Pharmaceuticals, Inc.

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