Patient burden of moderate to severe atopic dermatitis (AD): Insights from a phase 2b clinical trial of dupilumab in adults

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Background: The adult burden of atopic dermatitis (AD) is poorly characterized.

Objective: We sought to characterize AD burden in adults with moderate to severe disease from the patient’s perspective.

Methods: Patient-reported outcomes collected at screening in a phase 2b clinical trial of dupilumab included pruritus numeric rating scale, 5-Dimension Pruritus Scale, subjective components of SCORing AD, Patient-Oriented Eczema Measure, Hospital Anxiety and Depression Scale, Dermatology Life Quality Index, and 5-Dimension EuroQol.

Results: Most of the 380 patients had been living with AD for nearly all their lives, whereas approximately 40% were given a diagnosis as adults; 40.3% had asthma and 60.5% had other allergic conditions. Despite 48.2% of patients using systemic therapies in the past year, patients reported problems with itch frequency (85% of patients), duration (41.5% reported itching ≥18 h/d), and severity (6.5 of 10 on numeric rating scale); 55% reported AD-related sleep disturbances 5 d/wk or more. Hospital Anxiety and Depression Scale scores suggesting clinically relevant anxiety or depression were reported by 21.8% of patients. Quality of life was impaired on Dermatology Life Quality Index and 5-dimension EuroQol.

Limitations: This study had limited generalizability; conclusions may not reflect those with mild AD or not participating in a clinical trial.

Conclusions: Adults with moderate to severe AD report multidimensional burden including disease activity, patient-reported symptoms, comorbidities, and quality-of-life impact. (J Am Acad Dermatol 2016;74:491-8.)

Key words: adults; atopic dermatitis; burden of illness; patient-reported outcomes; pruritus; quality of life.

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Atopic dermatitis (AD) is an incurable, inflammatory skin disease characterized by skin barrier disruption and immune dysregulation largely mediated by type 2 helper T cells. Although AD onset generally occurs during early childhood, adult-onset disease is possible. Spontaneous remission may occur in late childhood, but AD is a chronic, lifelong condition for many patients.

The health and psychosocial burden associated with AD has primarily been characterized in the pediatric population. In adults, the burden has been suggested to include the presence of other type 2 helper T-driven comorbidities (asthma, allergies); daily effects associated with pruritus such as sleep disturbance and functional impairment; and secondary consequences including neuropsychiatric issues (anxiety, depression) and reduced health-related quality of life (HRQoL). Although the importance of capturing the full extent of this burden has been recognized, comprehensive information on the patient burden in adults with moderate to severe AD is limited. The objective of this analysis was to comprehensively evaluate the profile and overall health burden of adult patients with moderate to severe AD, emphasizing patient-reported outcomes in a prospective cohort.

**METHODS**

**Study design**

Data were from a multinational (Canada, the Czech Republic, Germany, Hungary, Japan, Poland, and the United States), dose-ranging, phase 2b clinical trial of dupilumab. Dupilumab, a fully human monoclonal antibody that targets the interleukin (IL)-4 receptor-α, blocks signaling of IL-4 and IL-13, thereby reducing the signs and symptoms of AD.

Details of the study along with primary efficacy and safety results have been reported. All study documents and procedures were approved by the appropriate institutional review boards/ethics committees at each study site. The study was registered with ClinicalTrials.gov, number NCT01859988; EudraCT number 2012-003651-11.

**Patients**

Required for study inclusion were age 18 years or older; the presence of AD defined by American Academy of Dermatology diagnostic criteria; chronic disease for 3 years or longer; Eczema Area and Severity Index (EASI) scores of 12 or higher at screening and 16 or higher at baseline; score 3 or higher (3 = moderate and 4 = severe) on the 0- to 4-point Investigator Global Assessment at screening and baseline; AD involvement covering 10% or more of body surface area at screening and baseline; and documented recent history (within 6 months before screening) of inadequate response to outpatient treatment with topical medications or patients for whom topical treatments were otherwise inadvisable. Analyses of disease burden were based on data collected at the screening visit, before study interventions, and included all randomized patients regardless of randomization group.

**Patient-reported outcomes**

The clinical SCORing AD (SCORAD) index includes 2 patient-reported outcomes, itch and sleep assessment over the previous 3 days, measured using a visual analog scale (VAS) (0 = no itch or sleep loss, 10 = worst imaginable itch or sleep loss). The pruritus numeric rating scale measures average and peak (worst) itch intensity for the previous 24 hours using an 11-point scale (0 = no itch to 10 = worst imaginable itch). The 5-dimension (5-D) Pruritus Scale assesses 5 dimensions of itch (degree, duration, direction, disability, and distribution) with a 2-week recall period. The Patient-Oriented Eczema Measure (POEM) evaluates time spent in the past week with AD signs and symptoms (itch, bleeding, weeping/oozing fluid, cracked skin, flaking skin, dry/rough skin) and their impact on sleep. POEM is scored on a 5-point scale (0 = no days to 4 = every day); score range is 0 to 28, and higher scores indicate greater impact. The Dermatology Life Quality Index (DLQI) is a 10-item questionnaire with Likert-type responses to evaluate the impact of skin conditions on HRQoL over the past week (score range 0-30; higher scores indicate greater impact).
usual activities, pain/discomfort, and anxiety/depression) with 3 response levels (no problem, some/moderate problems, or extreme problems/unable to do) with “today” as the reference period, and a VAS health state thermometer (0 = worst health to 100 = best health). Responses are used to generate an overall health index (0 = worst health to 1 = best health); in the current analysis, United Kingdom–based preferences were used to estimate this index.22 The HADS consists of subscales for anxiety and depression, each with 7 items and a score range of 0 to 21; scores 7 or lower are considered normal, 8 to 10 are borderline, and 11 or higher indicate clinical anxiety or depression.21

Statistics
Descriptive statistics were used throughout the analysis.

RESULTS
The population (N = 380) was predominantly male (61.6%), white (67.6%), and with a mean age of 37.0 (SD 12.2) years (Table I). The mean duration of AD was 27.6 years (SD 13.8), but some patients lived with AD for up to 65 years. Although 41.1% of the patients had AD since early childhood (age < 5 years), the age at diagnosis was 20 years or older in 37.1% of patients (Table I). The mean body surface area affected was approximately 50% (range 10%-99%), and atopic comorbidities such as asthma and allergic rhinitis were common (Table I). Scores for Investigator Global Assessment and POEM were consistent with moderate to severe disease (Table I).

Nearly all patients (97.4%) used at least 1 topical treatment for their AD during the past 3 months, primarily medium- to high-potency corticosteroids alone or in combination with other topical agents (94.5%) (data not shown). In addition, during the past year, almost half of the patients (48.2%) reported using at least 1 systemic treatment for AD; systemic corticosteroids were used by 36.1% of patients and cyclosporin by 12.9% (data not shown).

On the pruritus numeric rating scale, mean scores were the same for peak and average itch intensity (6.5 [SD 2.1]) and the mean pruritus VAS component of SCORAD was 6.9 (SD 2.3) (Table II). Itch intensity over the past 2 weeks on the 5-D Pruritus Scale was rated as severe by 46.3% of patients and an additional
14.2% rated their itch as unbearable (Table II). The majority (85.8%) of patients reported experiencing itch every day of the week (POEM), and 41.5% reported itching 18 h/d or more (5-D Pruritus Scale) (Table II).

Nearly all patients also reported the frequent occurrence of bleeding, oozing, cracking, flaking, or drying of their skin (Fig 1). Most skin symptoms occurred 5 d/wk or more in more than half the patients, with dry or rough skin the symptom reported most frequently by the highest proportion of patients (91.1%) (Fig 1).

AD and itching had a substantial impact on patient-reported sleep. On the 5-D Pruritus Scale, 68.2% of patients reported that itch delayed falling asleep and occasionally or frequently woke them up at night, and item 2 of POEM showed that 36.1% reported that their sleep was disturbed every night (Fig 2). Using a weighted average from the POEM item, sleep was disrupted an average of 4.4 nights over the previous week among all patients (data not shown). On the SCORAD self-reported sleep loss VAS, the mean score was 4.8 (SD 3.0) (data not shown).

The mean HADS total score was 12.2 (SD 7.4), and 21.8% of patients had subscale scores for anxiety and depression of 11 or higher, which is considered the cut-off value for a clinical case of anxiety or depression (Table III). In addition, 42.9% of patients had scores 8 or higher, indicating at least possible anxiety or depression. Anxiety symptoms were more common than depression symptoms (Table III). These proportions were consistent with the anxiety/depression dimension of the EQ-5D; 42.9% of patients reported being moderately anxious or depressed and 7.9% were extremely anxious or depressed (Table III).

The total DLQI score was 14.3 (SD 7.0) (data not shown), consistent with a very large impact on patients’ lives. Individual DLQI items showed that substantial proportions of patients reported frequent embarrassment or self-consciousness regarding their appearance, and interference with participation in relationships and daily life, including work/school (Fig 3). Furthermore, item 7 on the DLQI specifically

### Table II. Patient-reported itch

<table>
<thead>
<tr>
<th>Measure</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruritus NRS, mean (SD)</td>
<td>n = 370</td>
</tr>
<tr>
<td>Average itch score</td>
<td>6.5 (2.1)</td>
</tr>
<tr>
<td>Worst itch score</td>
<td>6.5 (2.1)</td>
</tr>
<tr>
<td>SCORAD pruritus VAS, mean (SD)</td>
<td>6.9 (2.3)</td>
</tr>
<tr>
<td>Degree of itch from 5-D Pruritus Scale, n (%)</td>
<td>n = 378</td>
</tr>
<tr>
<td>Unbearable</td>
<td>54 (14.2)</td>
</tr>
<tr>
<td>Severe</td>
<td>176 (46.3)</td>
</tr>
<tr>
<td>Moderate</td>
<td>132 (34.7)</td>
</tr>
<tr>
<td>Mild</td>
<td>16 (4.2)</td>
</tr>
<tr>
<td>Not present</td>
<td>0</td>
</tr>
<tr>
<td>Itch frequency per week from POEM, n (%)</td>
<td>n = 378</td>
</tr>
<tr>
<td>Every day</td>
<td>326 (85.8)</td>
</tr>
<tr>
<td>5-6 d</td>
<td>23 (6.1)</td>
</tr>
<tr>
<td>3-4 d</td>
<td>19 (5.0)</td>
</tr>
<tr>
<td>1-2 d</td>
<td>9 (2.4)</td>
</tr>
<tr>
<td>No days</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Duration of itch from 5-D Pruritus Scale, n (%)</td>
<td>n = 379</td>
</tr>
<tr>
<td>All day</td>
<td>113 (29.7)</td>
</tr>
<tr>
<td>18 to 24 h/d</td>
<td>45 (11.8)</td>
</tr>
<tr>
<td>12 to &lt;18 h/d</td>
<td>81 (21.3)</td>
</tr>
<tr>
<td>6 to &lt;12 h/d</td>
<td>69 (18.2)</td>
</tr>
<tr>
<td>&lt;6 h/d</td>
<td>71 (18.7)</td>
</tr>
</tbody>
</table>

NRS, Numeric rating scale; POEM, Patient-Oriented Eczema Measure; SCORAD, SCORing Atopic Dermatitis; VAS, visual analog scale.

*Percentages were calculated with N = 380 as the denominator.

![Fig 1. Atopic dermatitis. Frequency (days per week) of non-itch skin symptoms evaluated on the Patient-Oriented Eczema Measure. *Percentages were calculated with N = 380 as the denominator.](image)

![Fig 2. Atopic dermatitis. Impact of itch and atopic dermatitis on sleep, assessed using items on the 5-dimension (5-D) Pruritus Scale and the Patient-Oriented Eczema Measure (POEM). *Percentages were calculated with N = 380 as the denominator.](image)
B was 0.659 (SD 0.305) (data not shown). The mean score on the EQ-5D VAS was 60.0 (SD 22.9) and the overall health index score was 92.1%. The mean score on the EQ-5D VAS was 60.0 (SD 22.9). In contrast, most patients reported “no problem” with mobility (83.9%) and anxiety/depression. In contrast, most patients reported “no problem” with mobility (83.9%). The mean score on the EQ-5D VAS was 60.0 (SD 22.9) and the overall health index score was 92.1%. The mean score on the EQ-5D VAS was 60.0 (SD 22.9). In contrast, most patients reported “no problem” with mobility (83.9%).

**DISCUSSION**

Results of this analysis provide insight into the duration and dimensions of the patient burden associated with AD in adults, showing that AD has a profound negative impact on patients’ mental and physical functioning, reducing their activity and HRQoL. Notably, these patients had moderate to severe AD despite a high reliance on topical and systemic treatments.

Although diagnosis occurred in early childhood in most of the patients, the data indicate that AD is not just a disease of childhood. Many of the patients had been living with AD for nearly their entire lives, including 50% of patients who had been living with active disease for more than 27 years. Although AD has often been thought to be a disease that patients “grow out of,” these results and recent longitudinal data suggest otherwise. Interestingly, approximately 40% of these patients were given a diagnosis of AD as adults, a proportion higher than the 9% to 17% reported in the literature. Although age of diagnosis does not necessarily indicate age of onset, these data nevertheless suggest a need for further characterization of adult-onset AD.

Many of the patients were living with comorbid asthma and other allergic or atopic conditions. Such an association between AD and other atopic conditions has been recognized, and the presence of these conditions increases the disease burden, health care use, and complexity of patient management. Importantly, these comorbidities raise the possibility that all these conditions have a similar etiology driven by a common immune dysregulation (eg, excess type 2 helper T inflammation), and it is possible that a therapy with effects on comorbidities and AD may provide additional clinical benefits.

While skin symptoms including bleeding and cracked or flaky skin were frequently reported, itch was almost a constant presence, not only of duration, with almost two thirds (62.9%) of patients reporting itch 12 hours a day or more, but also of severity. Notably, itch severity was consistent whether measured using the pruritus numeric rating scale or the VAS component of SCORAD. Pruritus resulted in patient-reported sleep disturbances, consistent with data from a study that objectively measured sleep and showed that sleep disturbances were associated with itch. Itch and difficulty sleeping have previously been reported to be the most frequent symptoms in adults with AD. Loss of sleep may contribute to daytime sleepiness and fatigue, further reducing functional activities and adversely affecting mood and HRQoL because sleep likely has a reciprocal relationship with mental health.

The data also suggest that the mental health effects of AD are substantial and may be under-recognized. The current analysis shows that anxiety or depressive symptoms are present in approximately 43% of patients, similar to the 46% of patients with AD identified as having probable mood disorder in another study. In fact, approximately 22% of patients reported HADS scores...
clinically indicative of anxiety or depression, similar to a European study that reported clinical depression in 10.1% of patients with AD and clinical anxiety in 17.6%.8 Also consistent with previous observations,9,31 symptoms of anxiety were present in a higher proportion of patients than were depressive symptoms. This may reflect the psychological distress produced by both the stigma associated with visible AD skin lesions and the unpredictability of disease flares, and may be manifested by the high proportion of patients (61.6%) who reported being embarrassed by or self-conscious of their skin condition in this study. This psychological burden can further negatively impact mood and HRQoL.30,32 Indeed, suicidal ideation has been reported in 15% of patients in an AD population in Europe11 and up to 20% of individuals with severe disease.33-36

Patient HRQoL appeared to be considerably impaired, as assessed by both the DLQI and the EQ-5D. When compared with other dermatologic conditions, the mean DLQI score suggests that these patients with moderate to severe AD reported a more profound impact on HRQoL than patients with psoriasis (8.8), pruritus (10.3), and chronic urticaria (9.9).37 Although the mean score on the DLQI (14.3) for the study patients was midrange of the scale (0-30), this score is slightly higher than the mean of 12.2 (range 4.5-21.4) that was reported across AD studies in a review of the DLQI across dermatologic conditions.37 It should also be noted, however, that the more homogeneous population in the current study contrasts with other studies, which often consisted of pediatric and adult patients across disease severity levels.

The EQ-5D VAS score of 60.0 suggests a lower HRQoL than the 63.6 recently reported in a German AD population,38 and may reflect the moderate to severe AD inclusion criteria of the current study. Furthermore, the EQ-5D overall health index score of 0.659 is substantially lower than the normative values of 0.856, 0.867, and 0.929 which have been reported in United Kingdom, United States, and Japanese populations, respectively,39 and lower
than that reported in the United States for other symptomatic or chronic diseases, such as 0.834 for psoriasis-type conditions and 0.751 for diabetes.40 The EQ-5D domain most affected was pain/discomfort. Although pain is not typically reported as a key issue in AD, the presence of overlapping mechanisms between pain and itch,41 and the constancy of the reported itch in these patients, which could potentially result in neuroplastic change over time, suggests that further investigation into the relationship between itch and pain in AD may be warranted.

Limitations of this study include generalizability; conclusions may not necessarily apply to patients with mild disease or patients unwilling to participate in a clinical trial. In addition, this was an international study so we cannot exclude cultural differences that may have influenced responses to the patient-reported outcomes. Nevertheless, we used validated instruments that were translated into the appropriate languages for the countries in the study. Similarly, our use of the United Kingdom algorithm for estimating the EQ-5D may limit interpretability. Although the DLQI is specific for dermatologic conditions, the EQ-5D is generic and, therefore, it is possible that at least part of the reduction in HRQoL observed with this measure was a result of other comorbid conditions, such as asthma.

Overall, this comprehensive analysis provides a novel perspective on the multidimensional nature of the patient burden of moderate to severe AD in adults, of whom a substantial proportion were given a diagnosis as adults, indicating that AD is not only a disease of early childhood. This burden is manifested by patient-reported symptoms, comorbid conditions including a high rate of anxiety/depression, an apparent ineffective and potentially harmful medication burden, and lower HRQoL than in other dermatologic conditions. This burden, combined with the substantial proportion of patients requiring systemic corticosteroid therapy, a treatment discouraged by current treatment guidelines, highlights the need for novel therapeutics for this patient population. Management strategies should include more effective therapies directed at the underlying pathophysiology, the range of symptoms, and comorbid conditions, and should incorporate mental health support.

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