Dermatology Practical & Conceptual

Burden of Disease in the Real-Life Setting of Patients with Atopic Dermatitis: Italian Data From the MEASURE-AD Study

Giuseppe Argenziano[1], Santo Raffaele Mercuri[2], Paola Savoia[3], Paolo Amerio[4], Anna Belloni Fortina[5], Maria Rita Bongiorno[6], Maria Beatrice De Felici Del Giudice[7], Aurora Parodi[8], Nicola Pimpinelli[9], Luca Stingeni[10], Michela Ortoncelli[11], Giuseppe Stinco[12], Giuliana Gualberti[13], Anna Levi[13], Valeria Scuderi[13], Luca Bianchi[14], Giovanna Malara[15]

1 Dermatology Unit, Department of Mental and Physical Health and Preventive Medicine, University of Campania Luigi Vanvitelli, Naples, Italy
2 Unit of Dermatology, IRCCS San Raffaele Hospital, Milan, Italy
3 Department of Health Sciences, Università del Piemonte Orientale, Novara, Italy
4 Dermatologic Clinic, Department of Medicine and Aging Science and Dermatologic Clinic, University "G. d'Annunzio", Chieti-Pescara, Chieti, Italy
5 Unit of Pediatric Dermatology, Department of Medicine DIMED, University of Padua, Padua, Italy
6 Section of Dermatology, Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties, University of Palermo, Palermo, Italy
7 Dermatologic Unit, University Hospital of Parma, Department of Medicine and Surgery, Parma, Italy
8 Division of Dermatology, Department of Health Sciences (DISSAL), University of Genoa, Genoa Italy and Ospedale Policlinico San Martino IRCCS, Genoa, Italy
9 Dermatology Unit, Department Health Sciences, University of Florence, Florence, Italy
10 Dermatology Section, Department of Medicine and Surgery, University of Perugia, Perugia, Italy
11 Medical Sciences Department, Dermatologic Clinic, University of Turin, Turin, Italy
12 Institute of Dermatology, University of Udine, Udine, Italy
13 AbbVie SrL, Campoverde di Latina, Italy
14 Dermatology Unit, Tor Vergata University Hospital, Rome, Italy
15 UOC of Dermatology, Grande Ospedale Metropolitano "Bianchi Melacrino Morelli", Reggio Calabria, Italy

Key words: real-life, moderate-to-severe atopic dermatitis, burden, QoL measures

Citation: Argenziano G, Mercuri SR, Savoia P, et al. Burden of Disease in Real-Life Setting of Patients with Atopic Dermatitis: Italian Data From the MEASURE-AD Study. *Dermatol Pract Concept.* 2024;14(1):e2024079. DOI: https://doi.org/10.5826/dpc.1401a79

Accepted: September 24, 2023; **Published:** January 2024

Funding: AbbVie sponsored the study, contributed to the design; participated in data collection, analysis, and interpretation of the data, in writing, reviewing and approval of the publication. No honoraria or payments were made for the publication.

Competing Interests: Paolo Amerio has received honoraria and speaker fees for: AbbVie, Janssen, Novartis, Sanofi, Amgen. Anna Belloni Fortina has served as consultant and/or participated to advisory boards for Abbvie, Sanofi, Novartis, Cilag Janssen, Leopharma, Pfizer and Artsana. Nicola Pimpinelli has the following conflicts of interest to disclose: BMS (unrestricted educational grant), Kyowa Kirin (advisory board, unrestricted educational grant), Novartis (research grant), Pierre Fabre (speakers' bureau), Recordati Rare Diseases (speakers' bureau, unrestricted educational grant), Sanofi (speakers' bureau), Takeda (advisory board, unrestricted educational grant). Michela Ortoncelli has participated to advisory board and events for Abbvie, Sanofi, Lilly, Novartis, Leo Pharma. Aurora Parodi has participated to clinical studies for Abbvie, Almirall, Galderma, Pfizer, Novartis, Leo pharma, Eli Lilly, Amgen, UCB. Luca Stingeni has been principal investigator in clinical trials sponsored by and/or and has received personal fees from Abbvie, Celgene, Janssen, LeoPharma, Lilly, Novartis, Regeneron, Sanofi, outside the submitted work. Luca Bianchi has served as speaker and consultant for Abbvie, Novartis, Janssen-Cilag, Pfizer, UCB, Biogen, Leopharma, Sanofi, Eli Lilly, Sun Pharma, Sanitpharma outside the submitted work. Giuliana Gualberti and Anna Levi

are AbbVie employees and may own AbbVie stocks/options. Valeria Scuderi is a former employee of Abbvie, and she is now affiliated with Alfasigma SpA. All other authors have no conflict of interest to declare.

Authorship: All authors have contributed significantly to this publication.

Corresponding Author: Professor Giuseppe Argenziano, MD, PhD, Department of Dermatology, University of Campania "Luigi Vanvitelli", Via Sergio Pansini 5, 80131 Napoli, Italy Phone: +39-0815666828 FAX: +39-0815468759

Acknowledgments: The authors wish to thank Sara di Fino and Chiara Palladino, of AbbVie, for critical reading of the manuscript and Colin Gerard Egan (CE Medical Writing SRLS, Pisa Italy) for medical writing, funded by AbbVie.

ABSTRACT

Introduction: Atopic dermatitis (AD) is a chronic inflammatory skin disease that negatively impacts the quality of life and work productivity of patients.

Objectives: We sought to evaluate the real-world burden of AD patients in Italy.

Methods: This sub-analysis of the MEASURE-AD multicountry study conducted between December 2019-2020 included patients diagnosed with moderate-to-severe AD eligible for or receiving systemic therapy in the previous 6 months. During a single visit, physician and patient-reported questionnaires were used.

Results: A total of 118 adult patients were enrolled and 57.6% (N = 68) of patients had moderate-to-severe AD at the time of enrolment according to the Eczema Area and Severity Index. Sleep disorders interfered with daily function in the previous week in 58.5% (N = 69) of patients, pruritus was severe in 50% (N = 59) and 42.4% (N = 50) reported a flare lasting >7 days in the previous 6 months. According to the Dermatology Quality of Life Index, 37.3% (N = 44) of patients reported a severe impact of AD and approximately 10% had clinical depression/anxiety. Current drug therapy was considered inadequate in controlling AD in 26.3% (N=31) of patients. Work activity impairment was 38.6±31.7% and monthly AD-related expenses were 148.6±134.6 Euros per patient.

Conclusions: This real-life study documents a high burden of disease in patients with moderate-severe AD in Italy.

Introduction

Atopic dermatitis (AD) is a chronic, inflammatory, skin disorder associated with significant disease burden. The burden of AD mainly derives from signs and symptoms of AD which cause severe sleep loss in the first instance, then subsequently has a strong impact on quality of life (QoL), leading to the development of pathologies/conditions such as mental health disturbance, anxiety and depression as well as work/study impairment [1,2].

Consensus based European guidelines recommend that adults with severe AD whose symptoms are not adequately controlled with topical agents should be considered for systemic treatments as well as immunosuppressants, phototherapy, or short-term oral corticosteroids for the management of acute flares [3]. Systemic therapy can be useful to reduce the total amount of topical corticosteroids in patients who need large amounts of potent topical corticosteroids for large body areas over prolonged periods to control their AD.

Indeed, the area of systemic therapy for the treatment of AD has flourished in the past few years, as many new substances (including inhibitors of IL-4 and IL-13 signaling pathways as well as Janus kinase; JAK inhibitors) have been marketed, licensed, or are in the last stages of clinical development [3–5]. Development programs for these novel biologics are providing much better levels of evidence compared to older traditional drugs.

Substantial gaps in our understanding remain with regards to the overall burden of AD on patient health and wellbeing, particularly in patients with moderate-to-severe disease [6–9].

Recent studies in moderate-to-severe AD report the presence of a multidimensional disease burden [10–13] that includes other atopic comorbidities associated with pruritus such as sleep disturbance and functional impairment, and secondary consequences including neuropsychiatric issues (anxiety, depression) and reduced health related QoL (HRQoL) [1,14–16].

Nevertheless, few studies worldwide have specifically examined the burden of moderate-to-severe AD across a wide spectrum of QoL measures, particularly from the patients perspective [11,13,17–22].

Objectives

To address these gaps, this sub-analysis of the global cross-sectional MEASURE-AD study was performed on the

adult population in Italy to collect information on disease burden experienced by patients in terms of itching, skin pain, sleep and mental disturbance as well as work productivity and out-of-pocket expenses.

Methods

Study Design

The MEASURE-AD study is a multicenter, cross-sectional, observational study of patients with moderate-to-severe AD that aimed to assess the multidimensional burden of disease, treatment pattern, and health care resources. This sub-analysis of the MEASURE-AD study performed in Italy evaluated AD patients enrolled between December 2019 and December 2020 in a real-world setting.

Patients

Patients attending a routine visit, who fulfilled the following selection criteria were included: a confirmed diagnosis of AD in patients aged ≥18 years with moderate-to-severe AD, patients who are (i) current candidates for systemic therapy for AD, or (ii) currently receiving systemic therapy for AD, treatment history for the past 6 months; able to understand the questionnaires, consent to use and disclose personal health information and to participate in the study. Patients were excluded if they were currently participating in interventional clinical trial(s). The study was conducted in accordance with the declaration of Helsinki and approval was obtained by all the Local Ethics Committees (first approval from Comitato Etico Università degli Studi della Campania "Luigi Vanvitelli", Prot N.: 766, on 05/12/2019).

Outcome Measures

Disease Severity

The extent and severity of AD were evaluated by dermatologists through the Eczema Area and Severity Index (EASI) [23,24] score according to Chopra [25] and Leshem [24]. Patients self-reported AD symptoms through the Patient-Reported Eczema Measure (POEM) [26].

Itching/Pruritus

Numerical Rating Scales (0–10) for pruritus (Itch-NRS) and the 5-D pruritus scale were used to assess the level of pruritus [27,28].

Skin Pain

The ADerm-SS questionnaire was used to assess patient-reported skin pain [29].

Impact of AD on HRQoL

AD impact on health-related QoL was self-evaluated by patients through the Dermatology Quality of Life Index (DLQI) [30].

Patient-Reported Disease Control

Patient-reported disease control was assessed by asking patients to rate their degree of agreement with the validated statement, "I feel my current treatments are effective in controlling my atopic dermatitis." Patients were also asked to report the number and average duration of AD flares in the previous 6 months.

Patient-Reported Sleep

Specific sleep-related questions were used to assess the impact of AD on sleep. These included: 1) average number of hours slept per night in the past week, 2) average number of minutes needed to fall asleep per night in the past week, 3) number of nights in which sleep was disturbed over the past week, 4) sleep problems that interfered with daily function over the past week, 5) sleep problems that interfered with daily function over the past week.

The Atopic Dermatitis Impact Scale (ADerm-IS) questionnaire was also used to assess the impact of AD on sleep, daily activities and emotion [29].

Patient-Reported Mental Health

The Hospital Anxiety and Depression Scale (HADS) was used to assess Symptoms of anxiety and depression [31].

Impact of AD on Work Productivity

The Work Productivity and Activity Impairment Questionnaire–Atopic Dermatitis (WPAI-AD) was used to measure impairment due to AD [32,33]. Scores were calculated as percentages, with higher scores indicating greater work productivity loss and activity impairment.

Out-of-Pocket Expenses

Patients documented their treatment and other healthcare-related expenses each month (in Euro) due to their AD.

Statistical Analysis

Data are presented as mean and standard deviation for normally distributed variables or number and % for categorical variables. Statistical analysis was performed using SAS® Software (release 9.4, SAS Institute) on Microsoft Windows.

Results

Patient Characteristics

Baseline demographic and clinical characteristics of the study population are summarized in Table 1. Sixty-three (53.4%) patients were male and mean age was 37.7±15.4 years. The mean age at disease onset was 13.3±17.9 years and a family history of AD was seen in 44.1% (N =5 2) of patients. Most patients also had atopic comorbidities (78.8%; N = 93), the

Table 1. Baseline clinical characteristics of atopic dermatitis patients.

Clinical Characteristics	AD Patients (N = 118)
General	
Age (years)	37.7±15.4
Male gender, N (%)	63 (53.4)
BMI (kg/m^2)	23.8±3.7
Age of disease onset (years)	13.3±17.9
Age at diagnosis (years)	15.7±19.0
Familial history of AD, n (%)	52 (44.1)
Education, N (%)	
Primary school	14 (11.9)
Secondary school	68 (57.6)
University or a higher education	36 (30.5)
Comorbid diseases, N (%)	
Any atopic comorbidity	93 (78.8)
Any non-atopic comorbidity	40 (33.9)
Not in therapy for AD, N (%)	4 (3.4)
Treatment, N (%)	
Topical treatment	53 (44.9)
Current systemic treatment	91 (77.1)
Dupilumab	67 (56.8)
Cyclosporine	19 (16.1)
Systemic corticosteroids	4 (3.4)
Methotrexate	4 (3.4)
Phototherapy	5 (4.2)
Disease status	
BSA (%)	18.7±20.3
EASI score	11.2±11.5

AD = atopic dermatitis; BMI = body mass index; BSA = body surface area; EASI = eczema area and severity index.
Data are presented as number and % or mean ± SD.

most frequent being allergic rhinitis (48.3%; N = 57) or allergic asthma (33.9%; N = 40). Non-atopic comorbidities were also seen in approximately one-third of patients (33.9%; N = 40), the most frequent being hypertension, (12.5%; N = 15), anxiety (11.9%; N = 14), depression and diabetes (both 4.2%; N = 5).

Current Treatment

The average time taken from diagnosis of AD to first treatment was 139±177.4 months and to first systemic treatment was 231±169.4 months. Four patients (3.4%) were not receiving any treatment, while 53 patients (44.9%) were receiving topical treatment (Table 1). However, most patients (77.1%; N = 91) were currently receiving systemic treatment. Just over half of patients were being currently prescribed dupilumab (56.8%; N = 67), administered alone in 38 (32.2%) patients, in combination with topical therapy in 17 patients (14.4%) or in combination with topical and another systemic therapy in 1 (0.8%) patient.

Outcome Measures

Disease Severity

Mean EASI score was 11.2±11.5 (Table 1) and 57.6% (N = 68) patients were categorized as having moderate-to-severe AD according to Chopra (Figure 1A) while 53.4% (N = 63) patients were categorized as having moderate-to-severe AD according to Leshem (Figure 1B). Mean body surface area (BSA) was 18.7±20.3% (Table 1) and 40.7% (N=48) of patients were categorized as having moderate-to-severe AD according to Chopra BSA AD severity (Figure 1C) [25].

Sleep and the Impact of Itching/Pruritus

The average number of hours slept per night in the past week was 6.5±1.7 and the average time needed to fall asleep per night was 31.1±31.7 minutes. In the past week, the average number of days with disturbed sleep was 2.7±2.5 days and in 58.5% of patients (N = 69) sleep problems interfered with daily function (Figure 2A).

The patient-reported 5D pruritus scale revealed that 33.1% (N = 39) patients experienced delays falling asleep due to pruritus (Figure 2B).

Question 2 from the POEM questionnaire "Over the last week, on how many nights has your sleep been disturbed because of your eczema?" revealed that as many as 41.5% (N = 49) patients had disturbed sleep due to eczema (Figure 2C).

Mean scores for sleep, daily activities and emotional state domains according to the ADerm-IS questionnaire were similar (ranging from 11.8 to 13.9) and the total ADerm-IS score was 37.5±30.4 (Table 2). In terms of ADerm-IS single item scores, items relating to sleep disturbance were generally higher compared to other items evaluated.

Mean Itch-NRS was 5.4±3.4 and 65.3% (N = 77) of patients reported moderate or severe pruritus according to Vakharia scale (Figure 3A) [27].

Question 1 from the POEM questionnaire "Over the last week, on how many days has your skin been itchy because of your eczema?" showed that the majority of patients were affected by itch skin because of their eczema in the past week and 65.3% (N = 77) were itchy ≥3 days in the past week (Figure 3B).

Skin Pain

Mean score for ADerm-TSS-7 and ADerm-TSS-11 were 32.4±21.9 and 47.8±33.5 respectively (Table 3). Lowest mean scores for quantitative variables evaluated were from 4 (worst skin cracking) to highest of 5.4 (worst dry skin) and worst skin pain categories (7-10) accounted for 33.9%

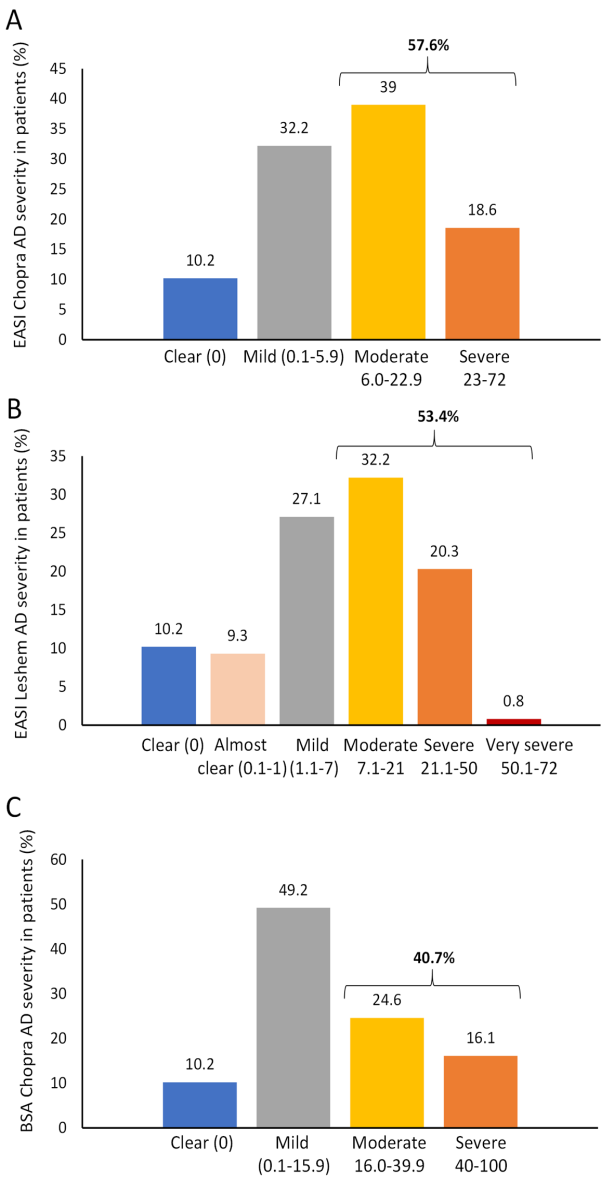

Figure 1. Disease severity in patients with AD. (A) Proportion of patients categorized as having clear, mild, moderate or severe AD according to EASI Chopra severity scale. (B) Proportion of patients categorized as having clear, mild, moderate, severe and very severe AD according to EASI Leshem severity scale. (C) Proportion of patients categorized as having clear, mild, moderate or severe AD according to BSA Chopra severity scale. The EASI score ranges from 0 to 72, and according to Chopra was categorized as follows: 0 = clear, 0.1–5.9 = mild, 6–22.9 = moderate and 23-72 = severe. The EASI score according to Leshem was categorized as follows: 0 = clear, 0.1–1.0 = almost clear, 1.1-7 = mild, 7.1–21 = moderate and 21.1-50 = severe, 50.1-72 = very severe. Data are presented as %.

AD = atopic dermatitis; BSA = body surface area; EASI = Eczema Area and Severity Index.

(N = 40) of patients and 51.7% (N = 61) rated their skin pain as ≥4.

Impact of AD on HRQoL

Overall mean DLQI score was 8.7±7.3 and the proportion of patients reporting a mild, moderate and severe impact of

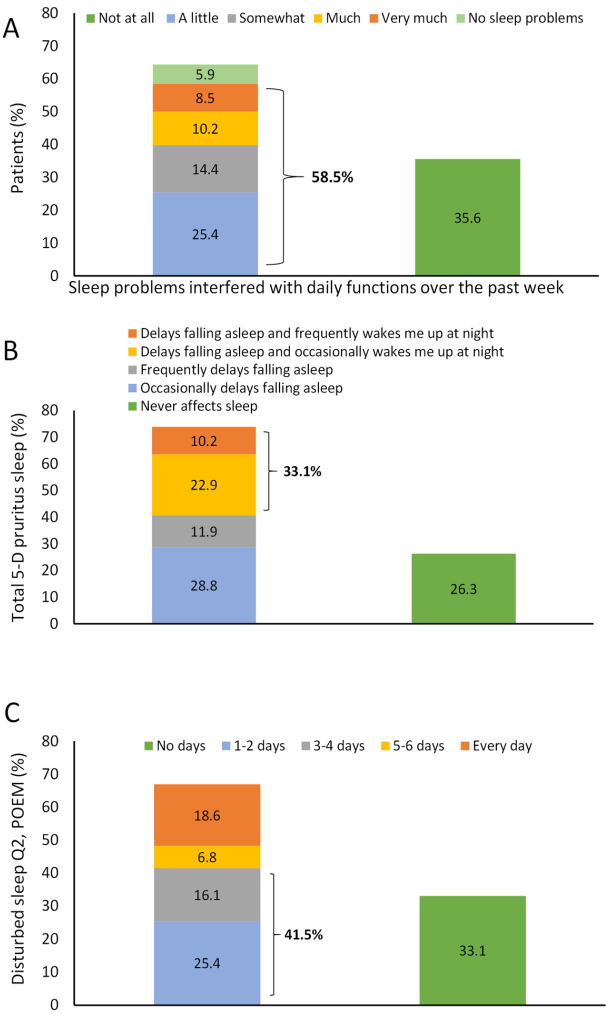

Figure 2. The impact of itching/pruritus on sleep in patients with AD. (A) Proportion of patients categorized to what extent sleep problems interfered with daily function overt the past week. (B) Proportion of patients categorized to what extent pruritis interfered with their sleep according to Total 5-D. (C) Proportion of patients categorized to what extent their sleep was disturbed (in number of days) according to question 2 of POEM questionnaire; "Over the last week, on how many nights has your sleep been disturbed because of your eczema?". POEM is a 7-item symptom inventory for eczema with a 1-week recall period. Scores range from 0–28, with higher scores indicating worse severity of disease. Data are presented as %.

AD = atopic dermatitis; POEM = Patient-Reported Eczema Measure.

AD on DLQI were 41.5% (N = 49), 21.2% (N = 25) and 37.3% (N = 44) respectively. In general, in >50% of patients, AD affected (a little or a lot/much) a physical, social, emotional, and personal issues for a wide range of DLQI items. The proportion of patients responding to the item "itchy, sore, painful, stinging skin" were 10.8%, 39.2% and 45.8% for "not at all", "a little" or "a lot/very much" respectively.

Patient-Reported Disease Control and Presence of Flares

For 68 (57.6%) patients their current drug therapy was considered effective, while 31 (26.3%) patients felt that

Table 2. Results for ADerm-IS

Variable	mean±SD
Quantitative variables	
Sleep domain score	11.9±10.2
Daily activities domain score	13.9±12.3
Emotional state domain score	11.8±10.3
ADerm-IS total score	37.5±30.4
ADerm-IS single items	
Difficulty falling asleep due to AD	3.7±3.3
Impact of AD on sleep	3.8±3.5
Bothered at night due to AD	4.4±3.9
AD limiting household activities	3.7±3.5
AD limiting physical activities	3.3±3.3
AD limiting social activities	3.3±3.4
Difficulty concentrating due to AD	3.7±3.3
Self-consciousness due to AD	4.0±3.6
Embarrassment due to AD	3.8±3.5
Sadness due to AD	4.1±3.8

The questionnaire was composed of 3 domains (sleep, daily activities and emotion) and an overall score as well as 10 single items (questions) based on the 3 domains. Three questions assessed the impact of AD over the previous 24 hours and 7 questions assessed the impact over the past 7 days. Sleep domain score = questions 1-3, Daily activities domain score = questions 4-7 and Emotional state domain score: questions 8-10. ADerm-IS total score: questions 1-10.

Each question displays a rating scale of answer options ranging from 0 to 10 with a higher score indicating a larger (negative) impact each score was calculated as sum of the contributing items. If a contributing value was missing the score could not be calculated.

AD = atopic dermatitis; SD = standard deviation.
ADerm-IS = Atopic Dermatitis Impact Scale.

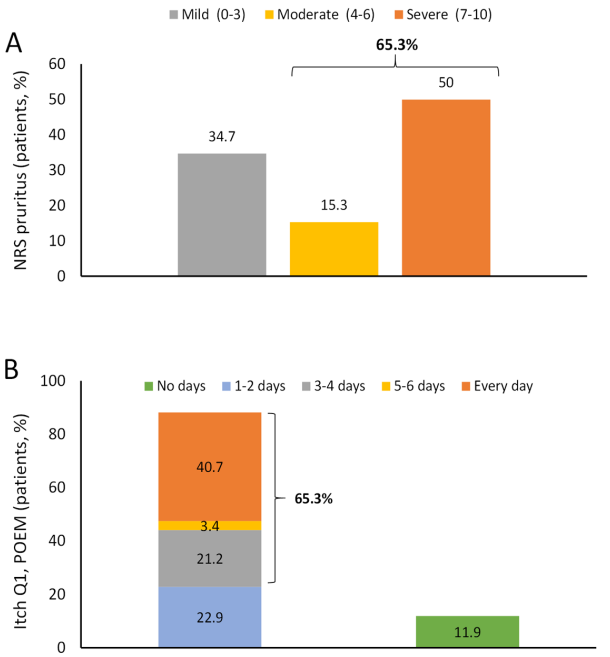

Figure 3. The extent of itching/pruritus experienced by patients with AD. (A) Proportion of patients categorised as having mild, moderate or severe pruritus according to NRS Vakharia scale. (B) Proportion of patients categorized by the number of days that they were affected by their pruritis in the past week according to question 1 of POEM questionnaire; "Over the last week, on how many days has your skin been itchy because of your eczema?". The level of pruritus was assessed in the following NRS categories according to Vakharia: mild: 0-3, moderate: 4-6 and severe: 7-10. The 5-D pruritus scale was a multidimensional questionnaire to measure itch. The five dimensions are duration, degree, direction, disability and distribution. 5-D scores ranged from 5 (no pruritus) to 25 (most severe pruritus).Data are presented as %.
AD = atopic dermatitis; NRS = Numerical Rating Scales; POEM = Patient-Reported Eczema Measure.

their current treatment was inadequate in controlling their AD. The mean number of flares reported in the previous 6 months was 3.5± 4.9 with over one-third (37.3%; N = 44) of patients having ≥3 flares in the previous 6 months. Mean duration of flares in the previous 6 months was 18±29.8 days and 42.4% (N = 50) of patients reported a flare duration greater than 7 days.

Patient-Reported Mental Health

Mean anxiety score (HADS-A) was 6.3±4.1 with 35.6% (N = 42) of patients having a HADS-A score of ≥8. Mean depression score (HADS-D) was 5.1±4 and 31.4% (N = 37) of patients had a HADS-D score of ≥8. The proportion of patients categorized as having normal, borderline or abnormal anxiety or depression according to HADS are summarized in Figure 4. Approximately two-thirds of patients reported no pathological signs of anxiety or depression while approximately 10% of patients reported having clinically relevant anxiety or depression.

Impact of AD on Work Productivity

Of the proportion of patients that were currently employed (N = 62; 52.5%), a mean presenteeism of 32.8±29.6%, mean absenteeism of 7.1±18.1% and a mean overall work productivity impairment of 36.1±30.9% were reported. The mean number of hours missed from work in the past 7 days was 1.7±5.6. Overall work activity impairment on daily life was 38.6±31.7%.

Out-of-Pocket Expenses

Monthly healthcare-related expenses and monthly costs for everyday necessities due to AD were 90.1±93.9 Euro and 56.7±63.1 Euro respectively with total monthly expenses of 148.6±134.7 Euro equating to 0.72±0.9% of annual family income.

Discussion

In AD, it is recognized that increased disease severity is frequently correlated with a worsening in QoL of the

Table 3. Results for ADerm-SS.

Variable	mean±SD
ADerm-TSS-7 score	32.4±21.9
ADerm-TSS-11 score	47.8±33.5
ADerm-SS single items	
Worst itch during sleep hours	4.7±3.7
Worst itch during awake hours	5.0±3.4
Worst skin pain	4.1±3.5
Worst skin cracking	4.6±3.3
Worst pain caused by skin cracking	4.0±3.4
Worst dry skin	5.4±3.4
Worst skin flaking	4.4±3.6
Worst rash	4.9±3.4
Worst skin thickening	4.2±3.4
Worst skin bleeding	3.0±3.3
Worst skin oozing	3.0±3.3

AD-Derm-TSS-7= 7-item total symptom based on questions 1-7. ADerm-TSS-11 score = 11-item total symptom based on questions 1-11. The ADerm-SS comprises 11 questions assessing experience of symptoms over the previous 24 hours. Each question displays a rating scale ranging from 0 (no symptom) to 10 (worst experience of symptom).

AD = atopic dermatitis; SD = standard deviation.
ADerm-IS = Atopic Dermatitis Impact Scale.

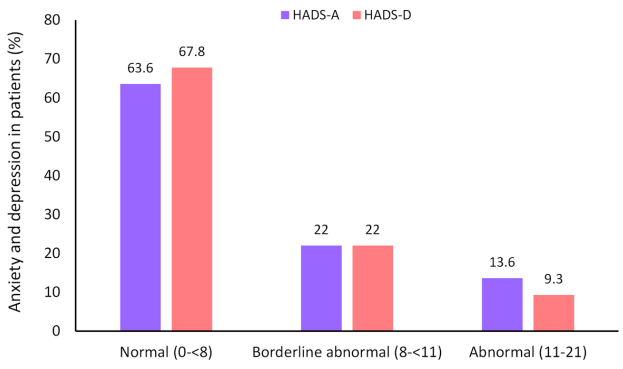

Figure 4. The impact of AD on anxiety and/or depression according to HADS questionnaire. HADS scores ranged from 0 to 21 for both the subscales (anxiety and depression), with 0-7 = normal, 8-10 = borderline abnormal (anxiety or depression related symptoms), and ≥11 indicating abnormal (ie clinically relevant depression or anxiety). Data are presented as %. AD = atopic dermatitis; HADS = Hospital Anxiety (HADS-A) and Depression (HADS-D) Scale.

patient [13,34]. Indeed, we observed that the proportion of patients with moderate (~30%) or severe (~20%) disease by the EASI or BSA closely reflect the proportion of patient with worse reported outcomes such as the proportion of patients affected by sleep problems (58.8%), severe pruritus (50.0%) and reporting a flare in the past week (42.4%). According to the DLQI, the impact of AD was reported to be moderate or severe in 21.2% or 37.3%, respectively. Similarly, about one-third of patients were judged as having clear or mild disease (by EASI) corresponding to a similar proportion of patients reporting no impact of their AD on sleep, pruritus or QoL measures.

Previous real-life studies in Italy have recently evaluated the association of factors affecting QoL in AD patients [17,20,21,35,36]. Ferrucci and colleagues evaluated factors associated with poor QoL in 300 AD patients with severe disease (mean EASI was 29.45±7.1 and DLQI was 16.8±6.8) [35]. Poor quality of sleep was found to be a predictor of anxiety symptoms, which is not surprising as anxiety disorders are frequently associated with insomnia [37]. Approximately half of patients had clinical anxiety or depressive symptoms (considering a HADS of ≥8) compared to approximately 30% in our study, likely reflecting the difference in the severity of AD in patients in their cohort. Similarly, in their study, poor sleep, itch and depression were correlated with each other, which again is to be expected and in turn to negatively impact upon daily activities and consequently QoL [38].

These results corroborate with observations by Miniotti et al where POEM, NRS for pruritus and sleep disturbance were significantly associated with DLQI and also in a small study by Milanesi et al where itch severity positively correlated with sleep quality [17,21].

In a post-hoc analysis of two randomized placebo-controlled phase-3 trials, Offidani et al., evaluated the improvement in signs and symptoms and QoL in patients with an EASI score of ≥20 to <24 or ≥24 treated with dupilumab for 16 weeks [36]. A weak correlation at baseline was observed between physician-assessed outcomes (reflected by EASI), patient-reported symptoms and QoL (reflected by pruritus NRS and DLQI) suggesting that patients with baseline EASI score of 20-24 can have substantial burden of disease and poor QoL. Indeed, patients with a substantially lower EASI (such as 11.2±11.5 in our study) can still be significantly burdened by their AD.

The impact of AD on work productivity observed in our study confirm evidence from previous studies of AD [39–41]. Indeed, we observed a significant impact of AD on both presenteeism and absenteeism with almost 2 hours missed from work in the past week.

In addition to the well-recognized work productivity and healthcare associated costs [42], the total monthly cost due to AD was estimated to be 148.6±134.7 Euro, similar to direct AD-related costs reported elsewhere [43].

Information with regards to the current treatment patients' satisfaction and their experience of this disease in terms of its multi-faceted impact on an array of socio-physical issues are still limited.

In our cross-sectional study we did observe that 37.3% of patients had ≥3 flares in the past 6 months and over half of

patients were affected by disturbed sleep experienced severe itching and markedly worse QoL. Over half of patients were assessed (by a dermatologist) as having moderate-severe disease corresponding to a similar proportion of patients receiving systemic treatment. However, in our cohort, we also observed long delays in diagnosis (~2 years), diagnosis to first treatment (~10 years) and to first systemic treatment (~19 years), pointing towards an important unmet need in the awareness of this skin disorder and the appropriate therapeutic management of these difficult-to-treat patients.

A recent nationwide campaign by The Italian Society of Dermatology and Venereology, provided direct access to 27 dermatologic centers dedicated to the management of AD and it was revealed that as many as 35% of patients received an incorrect diagnosis, almost 32% of patients were untreated (either with topical or systemic agents) whereas 44.3% used routine topical compounds, similar to the proportion in our study [22]. However, although mean EASI was similar in this cohort compared to our study (11.2), only 21.5% of patients had moderate-to-severe AD compared to ~55% in our study, where we specifically selected these patients. It is widely accepted that there is an unmet need in the management of AD and recent expert consensus has endeavored to provide guidance in this regard [6] in addition to recently published guidelines [3].

As well as studies undertaken in Italy, data are also available from other large real-life studies evaluating the burden and treatment patterns in AD patients from different countries [11,13,44]. Collectively, these studies and ours, reveal that patients with moderate-to-severe AD report significant disease burden, highlighting unmet treatment needs, with particularly attention focused on the lack of/underuse of systemic treatments.

Although not available at the time the present study was undertaken, it is worth noting that in recent years, other novel systemic therapies are available that have been shown to be effective in the management of pruritus [45-47]. Further studies are needed to understand how and to what extent novel targeted systemic therapy can improve patient reported outcomes in moderate-severe AD.

Strengths and Limitations

This was a cross-sectional observational study, and the long-term effects or trends were therefore not assessed. However, the sample size of 118 patients allowed us to provide a detailed snapshot of the current real-life management and patient-centered perspective of their disease burden in Italy.

This study assumed that most patients with moderate-to-severe AD would attend dermatology clinics or underwent office visits over a period of 6 months. Patients attending a routine visit were enrolled consecutively over a 6-month period, thereby reducing the potential for selection bias.

Patients were required to describe their sleep and QoL over the previous week, thereby introducing the potential for recall bias. In general, a major limitation of population-based studies of the burden of AD is that they solely rely on patient responses.

Strengths of our study lie in the multicenter design of current real-life management and treatment of adult patients with moderate-to-severe AD. Our findings grant a unique and in-depth perspective of the disease burden experienced by these patients.

Conclusions

This real-life study highlights the impact of moderate-to-severe AD experienced by patients, a burden that is extensive and varied. Besides physical symptoms such as pain and itching, patients also experience a negative impact of AD on their QoL as reflected by disturbed sleep, reduced workability, out-of-pocket costs, increased anxiety/depression, and reduced ability to carry out normal daily activities. Delays in diagnosis to first treatment and to first systemic therapy and a high proportion of patients still receiving topical treatment (44.9%) may explain in part why approximately one-quarter of patients were not satisfied with their current treatment. An awareness of the wide ranging and extensive burden from this chronic inflammatory illness are paramount in order to make important steps towards improving patient QoL.

References

1. Eckert L, Gupta S, Amand C, Gadkari A, Mahajan P, Gelfand JM. Impact of atopic dermatitis on health-related quality of life and productivity in adults in the United States: An analysis using the National Health and Wellness Survey. *J Am Acad Dermatol*. 2017;77(2):274-279.e3. DOI:10.1016/j.jaad.2017.04.019. PMID: 28606711.
2. Silverberg JI, Chiesa Fuxench ZC, Gelfand JM, et al. Content and construct validity, predictors, and distribution of self-reported atopic dermatitis severity in US adults. *Ann Allergy Asthma Immunol*. 2018;121(6):729-734.e4. DOI:10.1016/j.anai.2018.07.040. PMID: 30092267.
3. Wollenberg A, Kinberger M, Arents B, et al. European guideline (EuroGuiDerm) on atopic eczema: part I - systemic therapy. *J Eur Acad Dermatol Venereol*. 2022;36(9):1409-1431. DOI:10.1111/jdv.18345. PMID: 35980214.
4. Mostafa N, Phan K, Lai B, Smith SD. Comparing quality of life outcomes of JAK inhibitors and biological treatments for atopic dermatitis: a systematic review and network meta-analysis. *Expert Rev Clin Pharmacol*. 2021;14(11):1435-1444. DOI:10.1080/17512433.2021.1970529. PMID: 34410205.
5. Simpson EL, Papp KA, Blauvelt A, et al. Efficacy and Safety of Upadacitinib in Patients With Moderate to Severe Atopic

Dermatitis: Analysis of Follow-up Data From the Measure Up 1 and Measure Up 2 Randomized Clinical Trials. *JAMA Dermatology*. 2022;158(4):404-413. DOI:10.1001/jamadermatol.2022.0029. PMID: 35262646. PMCID: PMC8908226.

6. Patrizi A, Costanzo A, Patruno C, Busà VM, Chiricozzi A, Girolomoni G. Unmet needs in atopic dermatitis management: an expert consensus. *J Dermatolog Treat*. 2022;33(5):2459-2465. DOI:10.1080/09546634.2021.1967267. PMID: 34445932.
7. Drucker AM, Wang AR, Qureshi AA. Research Gaps in Quality of Life and Economic Burden of Atopic Dermatitis: The National Eczema Association Burden of Disease Audit. *JAMA Dermatol*. 2016;152(8):873-874. DOI:10.1001/jamadermatol.2016.1978. PMID: 27305113.
8. Kim JP, Chao LX, Simpson EL, Silverberg JI. Persistence of atopic dermatitis (AD): A systematic review and meta-analysis. *J Am Acad Dermatol*. 2016;75(4):681-687.e11. DOI:10.1016/j.jaad.2016.05.028. PMID: 27544489. PMCID: PMC5216177.
9. Lobefaro F, Gualdi G, Di Nuzzo S, Amerio P. Atopic Dermatitis: Clinical Aspects and Unmet Needs. *Biomedicines*. 2022;10(11):2927. DOI:10.3390/biomedicines10112927. PMID: 36428493. PMCID: PMC9687804.
10. Gisondi P. The multidimensional burden of psoriasis. *British Journal of Dermatology*. 2018;179(1):13-14. DOI:10.1111/bjd.16686. PMID: 30156285.
11. Kleyn CE, Barbarot S, Reed C, et al. Burden of Moderate to Severe Atopic Dermatitis in Adults from France, Italy, and the UK: Patient-Reported Outcomes and Treatment Patterns. *Dermatol Ther (Heidelb)*. 2022;12(8):1947-1965. DOI:10.1007/s13555-022-00777-z. PMID: 35913548. PMCID: PMC9357584.
12. Elsawi R, Dainty K, Smith Begolka W, et al. The Multidimensional Burden of Atopic Dermatitis Among Adults: Results From a Large National Survey. *JAMA Dermatol*. 2022;158(8):887-892. DOI:10.1001/jamadermatol.2022.1906. PMID: 35767267. PMCID: PMC9244770.
13. de Bruin-Weller M, Gadkari A, Auziere S, et al. The patient-reported disease burden in adults with atopic dermatitis: a cross-sectional study in Europe and Canada. *J Eur Acad Dermatol Venereol*. 2020;34(5):1026-1036. DOI:10.1111/jdv.16003. PMID: 31587373. PMCID: PMC7318704.
14. WAO. *World Allergy Organization (WAO) White Book on Allergy: Update 2013*. Available from: https://www.worldallergy.org/UserFiles/file/WhiteBook2-2013-v8.pdf, accessed on 12/10/2022
15. Simpson EL, Bieber T, Eckert L, et al. Patient burden of moderate to severe atopic dermatitis (AD): Insights from a phase 2b clinical trial of dupilumab in adults. *J Am Acad Dermatol*. 2016;74(3):491-498. DOI:10.1016/j.jaad.2015.10.043. PMID: 26777100.
16. Whiteley J, Emir B, Seitzman R, Makinson G. The burden of atopic dermatitis in US adults: results from the 2013 National Health and Wellness Survey. *Curr Med Res Opin*. 2016;32(10):1645-1651. DOI:10.1080/03007995.2016.1195733. PMID: 27240604.
17. Miniotti M, Lazzarin G, Ortoncelli M, Mastorino L, Ribero S, Leombruni P. Impact on health-related quality of life and symptoms of anxiety and depression after 32 weeks of Dupilumab treatment for moderate-to-severe atopic dermatitis. *Dermatol Ther*. 2022;35(5):e15407. DOI:10.1111/dth.15407. PMID: 35218275. PMCID: PMC9286472.
18. Ribero S, Giura MT, Viola R, et al. Effectiveness and safety of dupilumab for the treatment of atopic dermatitis in adult cohort: a real-life Italian tertiary centre experience. *J Eur Acad Dermatol Venereol*. 2020;34(8):e380-e383. DOI:10.1111/jdv.16219. PMID: 31960496.
19. Chiricozzi A, Gori N, Di Nardo L, et al. Therapeutic Impact and Management of Persistent Head and Neck Atopic Dermatitis in Dupilumab-Treated Patients. *Dermatology*. 2022;238(4):717-724. DOI:10.1159/000519361. PMID: 34710866.
20. Mastorino L, Rosset F, Gelato F, et al. Chronic Pruritus in Atopic Patients Treated with Dupilumab: Real Life Response and Related Parameters in 354 Patients. *Pharmaceuticals (Basel)*. 2022;15(7):883. DOI:10.3390/ph15070883. PMID: 35890180. PMCID: PMC9318403.
21. Milanesi N, Gola M, Cartocci A, et al. Effect of dupilumab on sleep disturbances in adult patients with severe atopic dermatitis. *Ital J Dermatol Venerol*. 2022;157(2):142-145. DOI:10.23736/S2784-8671.21.07072-9. PMID: 34282867.
22. Gori N, Chiricozzi A, Marsili F, et al. National Information Campaign Revealed Disease Characteristic and Burden in Adult Patients Suffering from Atopic Dermatitis. *J Clin Med*. 2022;11(17):5204. DOI:10.3390/jcm11175204. PMID: 36079131. PMCID: PMC9457191.
23. Hanifin JM, Thurston M, Omoto M, Cherill R, Tofte SJ, Graeber M. The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. EASI Evaluator Group. *Exp Dermatol*. 2001;10(1):11-18. DOI:10.1034/j.1600-0625.2001.100102.x. PMID: 11168575.
24. Leshem YA, Hajar T, Hanifin JM, Simpson EL. What the Eczema Area and Severity Index score tells us about the severity of atopic dermatitis: an interpretability study. *Br J Dermatol*. 2015;172(5):1353-1357. DOI:10.1111/bjd.13662. PMID: 25580670.
25. Chopra R, Vakharia PP, Sacotte R, et al. Severity strata for Eczema Area and Severity Index (EASI), modified EASI, Scoring Atopic Dermatitis (SCORAD), objective SCORAD, Atopic Dermatitis Severity Index and body surface area in adolescents and adults with atopic dermatitis. *Br J Dermatol*. 2017;177(5):1316-1321. DOI:10.1111/bjd.15641. PMID: 28485036.
26. Charman CR, Venn AJ, Ravenscroft JC, Williams HC. Translating Patient-Oriented Eczema Measure (POEM) scores into clinical practice by suggesting severity strata derived using anchor-based methods. *Br J Dermatol*. 2013;169(6):1326-1332. DOI:10.1111/bjd.12590. PMID: 24024631. PMCID: PMC3920642.
27. Vakharia PP, Chopra R, Sacotte R, et al. Severity strata for five patient-reported outcomes in adults with atopic dermatitis. *Br J Dermatol*. 2018;178(4):925-930. DOI:10.1111/bjd.16078. PMID: 29048751. PMCID: PMC5906166.
28. Elman S, Hynan LS, Gabriel V, Mayo MJ. The 5-D itch scale: a new measure of pruritus. *Br J Dermatol*. 2010;162(3):587-593. DOI:10.1111/j.1365-2133.2009.09586.x. PMID: 19995367. PMCID: PMC2875190.
29. Foley C, Tundia N, Simpson E, Teixeira HD, Litcher-Kelly L, Bodhani A. Development and content validity of new patient-reported outcome questionnaires to assess the signs and symptoms and impact of atopic dermatitis: the Atopic Dermatitis Symptom Scale (ADerm-SS) and the Atopic Dermatitis Impact Scale (ADerm-IS). *Curr Med Res Opin*. 2019;35(7):1139-1148. DOI:10.1080/03007995.2018.1560222. D. PMID: 30561230.

30. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)--a simple practical measure for routine clinical use. *Clin Exp Dermatol*. 1994;19(3):210-216. PMID: 8033378.
31. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand*. 1983;67(6):361-370. DOI:10.1111/j.1600-0447.1983.tb09716.x. PMID: 6880820.
32. Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. *Pharmacoeconomics*.1993;4(5):353-365.DOI:10.2165/00019053-199304050-00006. PMID: 10146874.
33. Reilly MC, Gooch KL, Wong RL, Kupper H, van der Heijde D. Validity, reliability and responsiveness of the Work Productivity and Activity Impairment Questionnaire in ankylosing spondylitis. *Rheumatology (Oxford)*. 2010;49(4):812-819. DOI:10.1093/rheumatology/kep457. PMID: 20100797.
34. Simpson EL, Guttman-Yassky E, Margolis DJ, et al. Association of Inadequately Controlled Disease and Disease Severity With Patient-Reported Disease Burden in Adults With Atopic Dermatitis. *JAMA Dermatol*. 2018;154(8):903-912. DOI:10.1001/jamadermatol.2018.1572. PMID: 29971354. PMCID: PMC6143024.
35. Ferrucci SM, Tavecchio S, Angileri L, Surace T, Berti E, Buoli M. Factors Associated with Affective Symptoms and Quality of Life in Patients with Atopic Dermatitis. *Acta Derm Venereol*. 2021;101(11):adv00590. DOI:10.2340/00015555-3922. PMID: 34518893. PMCID: PMC9455335.
36. Offidani A, Stingeni L, Neri I, et al. Dupilumab treatment induced similar improvements in signs, symptoms, and quality of life in adults with moderate-to-severe atopic dermatitis with baseline Eczema Area and Severity Index Score <24 or ≥24. *Ital J Dermatol Venerol*.2022;157(1):39-46.DOI:10.23736/S2784-8671.21.06952-2. PMID: 33878856.
37. Buoli M, Grassi S, Serati M, Altamura AC. Agomelatine for the treatment of generalized anxiety disorder. *Expert Opin Pharmacother*. 2017;18(13):1373-1379. DOI:10.1080/14656566.2017.1359257. PMID: 28730851.
38. Weidinger S, Beck LA, Bieber T, Kabashima K, Irvine AD. Atopic dermatitis. *Nat Rev Dis Primers*. 2018;4(1):1. DOI:10.1038/s41572-018-0001-z. PMID: 29930242.
39. Andersen L, Nyeland ME, Nyberg F. Increasing severity of atopic dermatitis is associated with a negative impact on work productivity among adults with atopic dermatitis in France, Germany, the U.K. and the U.S.A. *Br J Dermatol*. 2020;182(4):1007-1016. DOI:10.1111/bjd.18296. PMID: 31260080. PMCID: PMC7187138.
40. Holm EA, Esmann S, Jemec GBE. The handicap caused by atopic dermatitis--sick leave and job avoidance. *J Eur Acad Dermatol Venereol*. 2006;20(3):255-259. DOI:10.1111/j.1468-3083.2006.01416.x. PMID: 16503882.
41. Stingeni L, Belloni Fortina A, Baiardini I, Hansel K, Moretti D, Cipriani F. Atopic Dermatitis and Patient Perspectives: Insights of Bullying at School and Career Discrimination at Work. *J Asthma Allergy*. 2021;14:919-928. DOI:10.2147/JAA.S317009. PMID: 34321892. PMCID: PMC8312319.
42. Augustin M, Misery L, von Kobyletzki L, Armario-Hita J c., Mealing S, Redding M. Unveiling the true costs and societal impacts of moderate-to-severe atopic dermatitis in Europe. *J Eur Acad Dermatol Venereol*. 2022;36 Suppl 7:3-16. DOI: 10.1111/jdv.18168. PMID: 35801296.
43. Sciattella P, Pellacani G, Pigatto PD, et al. The burden of atopic dermatitis in adults in Italy. *G Ital Dermatol Venereol*. 2020;155(1):19-23. DOI:10.23736/S0392-0488.19.06430-7. PMID: 31525844.
44. Augustin M, Costanzo A, Pink A, et al. Real-World Treatment Patterns and Treatment Benefits among Adult Patients with Atopic Dermatitis: Results from the Atopic Dermatitis Patient Satisfaction and Unmet Need Survey. *Acta Derm Venereol*. 2022;102:adv00830. DOI:10.2340/actadv.v102.3932. PMID: 36479885. PMCID: PMC10508272.
45. Ferrucci SM, Tavecchio S, Marzano AV, Buffon S. Emerging Systemic Treatments for Atopic Dermatitis. *Dermatol Ther (Heidelb)*. 2023;13(5):1071-1081. DOI:10.1007/s13555-023-00920-4. PMID: 37072648. PMCID: PMC10149421.
46. Silverberg J i., Thyssen J p., Fahrbach K, et al. Comparative efficacy and safety of systemic therapies used in moderate-to-severe atopic dermatitis: a systematic literature review and network meta-analysis. *J J Eur Acad Dermatol Venereol*. 2021;35(9):1797-1810. DOI: 10.1111/jdv.17351. PMID: 33991374. PMCID: PMC8453983.
47. Blauvelt A, Teixeira HD, Simpson EL, et al. Efficacy and Safety of Upadacitinib vs Dupilumab in Adults With Moderate-to-Severe Atopic Dermatitis: A Randomized Clinical Trial. *JAMA Dermatology*. 2021;157(9):1047-1055. DOI:10.1001/jamadermatol.2021.3023 PMID: 34347860. PMCID: PMC8340015.