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ORIGINAL RESEARCH

Real-World Clinical, Psychosocial, and Economic Burden of Atopic Dermatitis: Results From the ESSENTIAL AD Multicountry Study

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ABSTRACT

Introduction: Limited real-world evidence exists about the burden of atopic dermatitis (AD) in patients receiving systemic or non-systemic therapies in clinical practices. ESSENTIAL AD was an observational study that aimed to fill this information gap.

Methods: ESSENTIAL AD enrolled (September 2021–June 2022) adult patients with physician-confirmed AD that was routinely managed with systemic and non-systemic treatment in a real-world setting from 15 countries in Eastern Europe, the Middle East, and Africa. Primary out-

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come variables were Eczema Area and Severity Index (EASI), SCORing Atopic Dermatitis (SCORAD), and Dermatology Life Quality Index (DLQI) assessed during one office visit.

Results: A total of 799 enrolled patients fulfilled selection criteria and were included in the study. Patients mean (standard deviation [SD]) age was 36.3 (14.4) years, 457 (57.2%) were female, and the majority of patients were white (647 [81.0%]). Mean (SD) time since AD diagnosis was 17.6 (15.2) years (median 16.5; interquartile range [IQR] 3.3–26.8). The mean (SD) EASI, SCORAD, and DLQI total scores were 11.3 (11.3 [median 8.1; IQR 3.6–15.8]), 37.8 (17.9 [median 35.5; IQR 24.2–49.0]), and 10.6 (7.2 [median 10.0; IQR 5.0–15.0]), respectively. Patients receiving systemic treatment had significantly higher disease burden (mean [SD] EASI 13.3 [13.0]; median [IQR] 9.6 [3.9–17.9]) versus non-systemic treatment (mean [SD] 9.3 [8.7]; median [IQR] 6.8 [3.0–13.2]; $P < 0.0001$). Results were similar for SCORAD (39.9 [19.6] vs 35.6 [15.7]; median [IQR] 38.6 [24.7–53.1] vs 32.6 [23.9–44.6]; $P = 0.0017$), and DLQI total scores (11.4 [7.4] vs 9.9 [6.9]; median [IQR] 11.0 [5.0–16.0] vs 9.0 [5.0–14.0]; $P = 0.0033$, respectively).

Conclusion: Patients with AD continue to have substantial disease burden despite treatment with systemic therapy, suggesting that a need for effective disease management remains, including effective therapies that improve psychological outcomes and reduce economic burden of AD, in Eastern Europe, the Middle East, and Africa.

PLAIN LANGUAGE SUMMARY

Patients with atopic dermatitis often suffer from debilitating symptoms that impact their everyday lives. Although several treatment options are available, many patients continue to experience symptoms of disease. The ESSENTIAL AD study assessed burden of atopic dermatitis in patients receiving systemic and/or non-systemic therapies in real-life clinical practices across 15 countries in Eastern Europe, the Middle East, and Africa. The results of the study demonstrated that adult patients with atopic dermatitis continue to have substantial disease burden regardless of treatment with systemic therapy or non-systemic therapy. The findings suggest that optimal management of atopic dermatitis needs to be reassessed in Eastern Europe, the Middle East, and Africa, especially as new, more effective treatment options become available to patients.

Keywords: Atopic dermatitis; Disease burden; Global; Real-world; Treatment patterns

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Key Summary Points

Why carry out this study?

Limited real-world evidence exists about burden of atopic dermatitis (AD) in patients receiving either systemic or non-systemic therapies in clinical practices.

ESSENTIAL AD was an observational study that assessed disease burden in adult patients with physician-confirmed AD who were either currently treated with or prescribed on the day of the study visit any systemic and/or non-systemic therapy for AD (either as monotherapy or combination therapy) in a real-world setting in Eastern Europe, the Middle East, and Africa.

What was learned from this study?

Patients with AD continue to have substantial disease burden regardless of treatment with systemic therapy or non-systemic therapy.

Patients receiving systemic therapy had significantly higher disease burden, suggesting that patients with more severe disease were more likely to be treated with systemic therapy.

Overall, these results suggest that a significant unmet need remains for optimal AD management in Eastern Europe, the Middle East, and Africa.

INTRODUCTION

Atopic dermatitis (AD) is a common inflammatory skin disease characterized by the development of highly pruritic eczematous lesions and considerable quality of life and socioeconomic impact on patients and their families [1, 2]. The optimal management of AD involves the elimination of exacerbating factors, restoration of the skin barrier function and hydration of the skin, as well as patient education and pharmacologic treatment of skin inflammation [3]. However, despite treatment, AD often results in considerable physical, psychological, and socioeconomic burden on patients as demonstrated in the recent global real-world MEASURE-AD study in adolescent and adult patients with moderate-to-severe AD who were receiving or were candidates for systemic therapy [4].

However, limited real-world evidence exists about current AD severity and activity as well as healthcare costs in patients receiving either systemic or non-systemic therapies, including patients who were well managed with their current therapy, in clinical practices.

ESSENTIAL AD was an observational study that aimed to fill this information gap by characterizing the current state of AD among patients from Eastern Europe, the Middle East, and Africa who were routinely managed with systemic and non-systemic treatment in a real-world setting.

METHODS

Study Design and Participants

ESSENTIAL AD was an epidemiological, multicountry, cross-sectional and retrospective chart review observational study. Data were collected during a single visit in 15 countries across Eastern Europe, the Middle East, and Africa (Algeria, Bulgaria, Czech Republic, Egypt, Estonia, Hungary, Kuwait, Latvia, Lithuania, Poland, Romania, Russia, Slovakia, South Africa, and United Arab Emirates).

The study consecutively enrolled adults (aged $\geq$ 18 years) with an AD diagnosis confirmed by a specialist who were attending a routine clinic visit in clinics and offices over a period of approximately 9 months. Patients currently treated with any systemic and/or non-systemic therapy for AD (either as monotherapy or combination therapy) or patients prescribed any systemic and/or non-systemic therapy for AD (either as monotherapy or combination therapy) on the day of the study visit were eligible. Patients who were currently receiving treatment with any investigational drug, device,

or intervention, or had received any investigational product within 1 month or 5 half-lives of the investigational agent (whichever was longer) prior to enrollment were excluded.

This study was conducted in compliance with the Declaration of Helsinki, applicable local laws, and regulations. Notifications/submissions to the responsible ethics committees (see Table S1 in the Supplementary Material for details), health institutions, and/or competent authorities were performed as required by applicable local laws and regulations. Prior to enrollment, all patients gave written informed consent.

Variables

Primary outcome variables were Eczema Area and Severity Index (EASI), SCORing Atopic Dermatitis (SCORAD), and Dermatology Life Quality Index (DLQI) total scores, all measured at enrollment. In addition, proportion of patients with different severity categories of EASI, SCORAD, and DLQI were assessed.

Secondary variables were Worst Pruritus-Numerical Rating Scale (WP-NRS) score, the Work Productivity and Activity Impairment (WPAI)-AD total score, current treatments, clinical courses of AD (seasonal, episodic [moderate or severe], consistent, and consistent with flares), flares in the past 12 months (flare was defined as one or more consecutive days with significant worsening of symptoms requiring escalation of treatment or additional medical consultation), routine healthcare visits and acute care visits due to AD in the last 12 months, and out-of-pocket expenses (i.e., average monthly expenses evaluated by patient) in US dollars (USD).

Statistical Analyses

Quota sampling was used to achieve a balanced distribution in receiving systemic therapy (including combination therapy) for approximately 50% of patients and non-systemic therapy for approximately 50% of patients. Sample size was justified by precision analysis based on the primary variables (EASI, SCORAD, and DLQI total scores). According to the global MEASURE AD study [4], standard deviations (SDs) of these three variables were 12.8, 20.9, and 7.8, respectively. With a proposed 770 patients, the precisions for EASI, SCORAD, and DLQI total scores were 0.904, 1.476, and 0.551, respectively, calculated from a two-sided test. These precisions were considered high from a clinical perspective and were sufficient to provide robust descriptive estimates of observed characteristics of primary and secondary variables in the overall study population as well as subgroups of interest.

Descriptive statistics were provided for all demographic, clinical characteristics, treatment patterns, and quality-of-life (QoL) variables. Subgroup analysis by systemic (including combination treatment) and non-systemic therapy was conducted. Comparison between subgroups was done using a Kruskal–Wallis test for continuous variables and a Pearson's chi-square test for categorical variables. For rate estimation variables, negative binomial regression was used.

RESULTS

In total, 801 patients from 15 countries provided signed informed consent to participate; of these, 799 fulfilled all patient selection criteria and were included in the full analysis set (FAS). Data were collected between September 21, 2021, and June 29, 2022. The mean (SD) age of study participants was 36.3 (14.4) years, 457 (57.2%) of patients were female, and the majority of patients were white (647 [81.0%]; Table 1). At the time of the study visit, patients had a long AD disease history, with a mean (SD) time since AD diagnosis of 17.6 (15.2) years (median 16.5; interquartile range [IQR] 3.3–26.8 years).

Patients were from Russia (125 [15.6%]), Egypt (100 [12.5%]), Romania (100 [12.5%]), Bulgaria (70 [8.8%]), United Arab Emirates (69 [8.6%]), Czech Republic (68 [8.5%]), South Africa (51 [6.4%]), Poland (50 [6.3%]), Hungary (40 [5.0%]), Kuwait (40 [5.0%]), Slovakia (24 [3.0%]), Estonia (20 [2.5%]), Lithuania (20

Table 1 Baseline patient demographics and characteristics

	Total population (n = 799)	Systemic therapy users (n = 403)	Non-systemic therapy users (n = 396)	P value
Age at consent, years				0.9355
Mean (SD)	36.3 (14.4)	36.4 (14.4)	36.2 (14.4)	
Median (IQR)	33.0 (25.0–45.0)	33.0 (25.0–45.0)	33.0 (25.0–45.0)	
Female, n (%)	457 (57.2)	205 (50.9)	252 (63.6)	**0.0003**
Race, n (%)				0.7089
White	647 (81.0)	327 (81.1)	320 (80.8)	
Asian	115 (14.4)	57 (14.1)	58 (14.6)	
Black	19 (2.4)	8 (2.0)	11 (2.8)	
Other	18 (2.3)	11 (2.7)	7 (1.8)	
Employed, n (%)	489 (61.7)	257 (64.4)	232 (58.9)	0.4512
Time since AD diagnosis, years				0.0576
Mean (SD)	17.6 (15.2)	18.5 (15.4)	16.6 (15.0)	
Median (IQR)	16.5 (3.3–26.8)	17.7 (4.0–26.8)	15.5 (2.4–26.7)	
Time since AD diagnosis, n (%)				**0.0446**
0 years	63 (9.0)	20 (5.6)	43 (12.3)	
$\geq$ 10 years	429 (61.0)	224 (63.3)	205 (58.7)	
Current therapy, n (%)				
Systemic monotherapy or in combination	403 (50.4)	403 (100.0)	N/A	
Topical monotherapy or in combination	710 (88.9)	339 (84.1)	371 (93.7)	< **0.0001**
Non-pharmacological therapy	665 (83.2)	328 (81.4)	337 (85.1)	0.1603
Any comorbidity	295 (36.9)	155 (38.5)	140 (35.4)	0.3627
Most common comorbidities[a]				
Asthma	83 (10 .4)	49 (12.2)	34 (8.6)	
Hypertension	67 (8.4)	33 (8.2)	34 (8.6)	
Rhinitis allergic	51 (6.4)	21 (5.2)	30 (7.6)	
Type 2 diabetes mellitus	25 (3.1)	14 (3.5)	11 (2.8)	
Hypersensitivity	19 (2.4)	11 (2.7)	8 (2.0)	
Hypothyroidism	17 (2.1)	8 (2.0)	9 (2.3)	

Table 1 continued

	Total population (n = 799)	Systemic therapy users (n = 403)	Non-systemic therapy users (n = 396)	P value
Conjunctivitis allergic	16 (2.0)	8 (2.0)	8 (2.0)	
Diabetes mellitus	12 (1.5)	3 (0.7)	9 (2.3)	

AD atopic dermatitis, *IQR* interquartile range, *JAK* Janus kinase, *N/A* not applicable, *SD* standard deviation
[a]Occurring in ≥ 2.0% of patients in either subgroup

[2.5%]), Algeria (12 [1.5%]), and Latvia (10 [1.3%]).

Among the 799 patients, 403 (50.4%) patients received systemic therapy (including combination) and 396 (49.6%) were receiving non-systemic therapy (Table 1). The most frequently reported current pharmacological systemic treatments were oral antihistamines (28.9%), systemic corticosteroids (12.5%), and biological agents (11.3%), and only 2.5% of patients were receiving Janus kinase (JAK) inhibitors (Fig. 1). In the last 12 months prior to the study visit, only 4.0% of patients received biologic agents and 1.6% received JAK inhibitors. The median (IQR) time since prescription of current treatment was longer in patients treated with systemic therapy (including combination therapy) than in patients treated with non-systemic therapy (0.95 [0.0–5.0] vs 0.03 [0.0–1.8] months; $P < 0.0001$).

Most patients (88.9%) were treated with pharmacological non-systemic (topical) treatment. The most frequently reported current pharmacological non-systemic treatments were topical corticosteroids (77.2%), topical calcineurin inhibitors (31.5%) and topical antimicrobials (10.9%; Fig. 1). The most common non-pharmacological therapy was moisturizers (80.7%).

Overall, 295 (36.9) patients had at least one comorbidity; the most common comorbidities were asthma (83 [10.4%]) and hypertension (67 [8.4]; Table 1). No significant difference was observed between systemic and non-systemic treatment groups in comorbidities.

Primary Variables: EASI, SCORAD, DLQI

The mean (SD) EASI, SCORAD, and DLQI total scores at the study visit were 11.3 (11.3 [median 8.1; IQR 3.6–15.8]), 37.8 (17.9 [median 35.5; IQR 24.2–49.0]), and 10.6 (7.2 [median 10.0; IQR 5.0–15.0]), respectively (Fig. 2). Most patients had mild (38.0%) or moderate (39.4%) disease per EASI severity category with severe/very severe AD reported in 13.3% and 1.4% of patients, respectively; the remainder of patients were in the "almost clear" (6.6%) or "clear" (1.3%) categories (Fig. 2). Current AD severity evaluated by the SCORAD categories [5] was mild in 27.0% of patients, moderate in 49.3% of patients, and severe in 23.7% of patients. When assessing the current impact of AD on DLQI, 9.6% of patients reported no impact, 18.9% of patients reported small impact, 25.3% of patients reported moderate impact, 34.8% of patients reported very large impact, and 11.4% of patients reported extremely large impact.

When assessed by systemic treatment versus non-systemic treatment users, EASI (mean [SD] 13.3 [13.0] vs 9.3 [8.7]; median [IQR] 9.6 [3.9–17.9] vs 6.8 [3.0–13.2]; $P < 0.0001$), SCORAD (39.9 [19.6] vs 35.6 [15.7]; median [IQR] 38.6 [24.7–53.1] vs 32.6 [23.9–44.6]; $P = 0.0017$), and DLQI total scores (11.4 [7.4] vs 9.9 [6.9]; median [IQR] 11.0 [5.0–16.0] vs 9.0 [5.0–14.0]; $P = 0.0033$) were significantly higher among those receiving systemic versus non-systemic therapy (Fig. 3).

Secondary Variables

The mean (SD) WP-NRS score at the visit was 5.3 (2.7), indicating a moderate itch severity

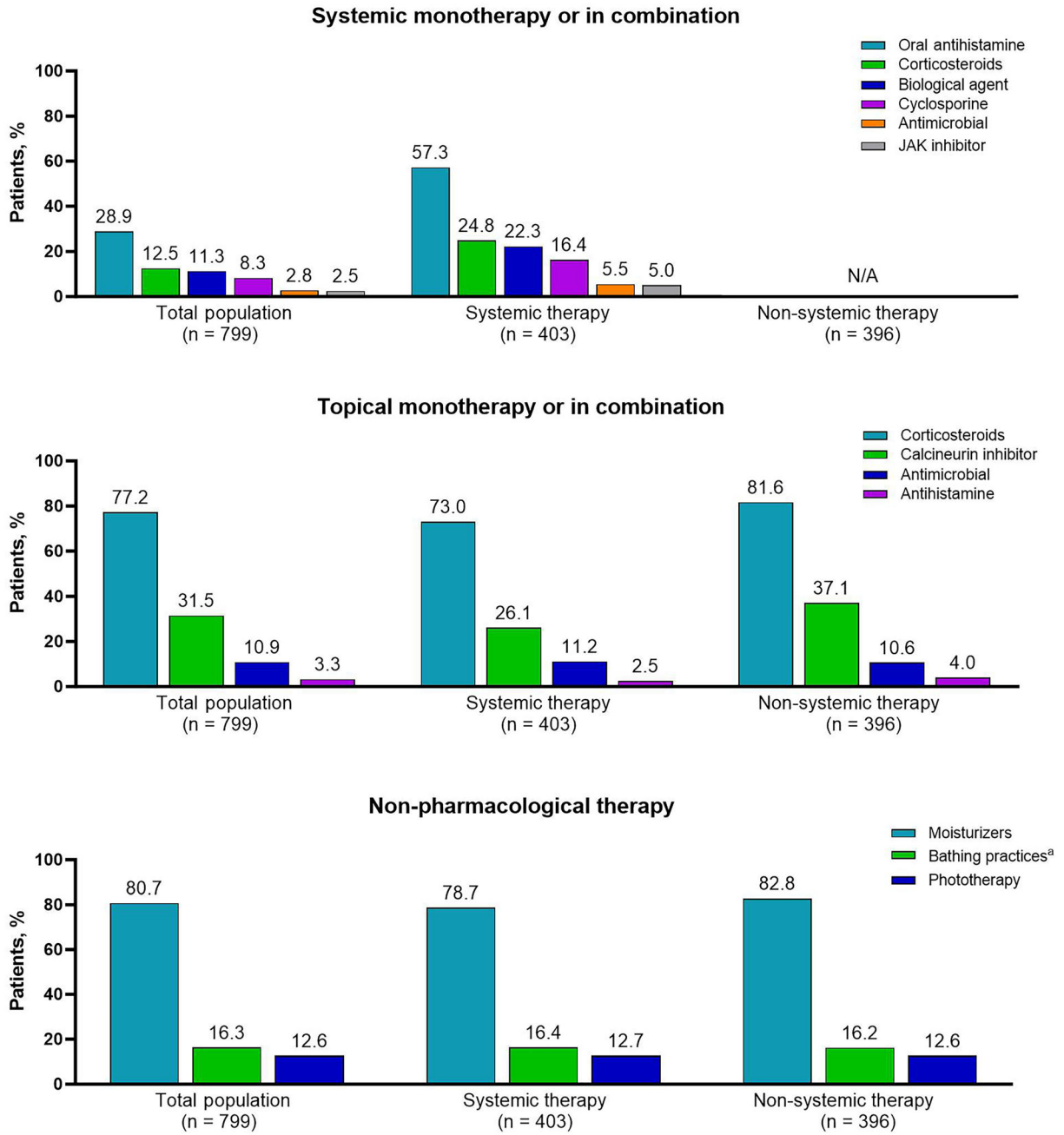

Fig. 1 Current treatments in the total population, systemic therapy group and non-systemic therapy group. [a]Including additives. *JAK* Janus kinase, *N/A* not applicable

(Table 2); median (IQR) WP-NRS was 5.0 (3.0–7.0). A mean (SD) overall work productivity loss of 35.1% (29.9%; median 30.0 [IQR 10.0–50.0]) was observed in employed adults (n = 502) and mean (SD) activity impairment of 35.7% (28.3%; median 30.0 [IQR 10.0–60.0]) in the total population. Overall, 775 patients reported their flare frequency; among these, 89.0% reported flares in the last 12 months (average of 3.8 AD flares in the previous 12 months; Table 2). The estimated flare rate (95% confidence interval [CI]) was 3.8 (3.6–4.1)

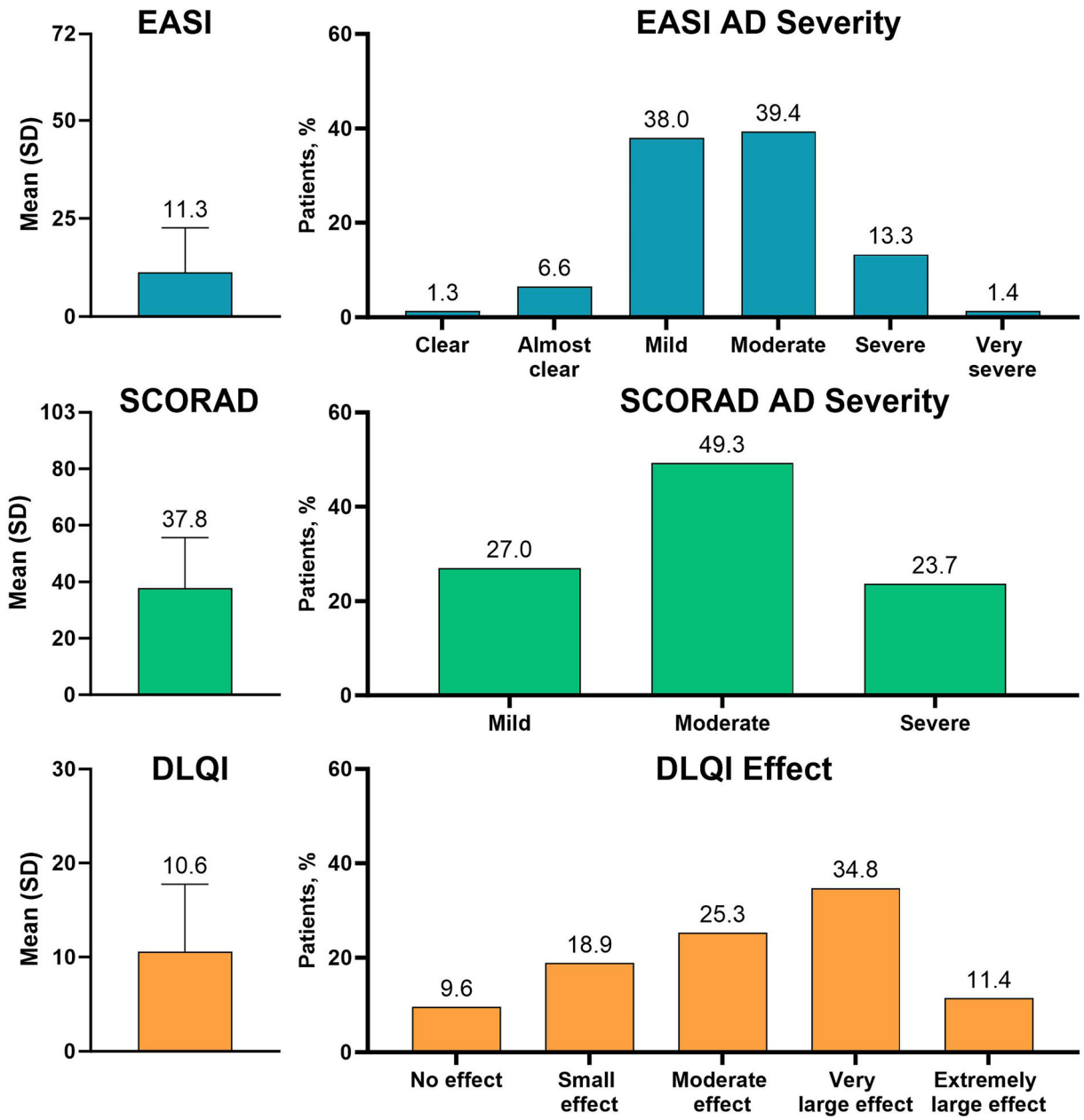

Fig. 2 Primary variables of EASI, SCORAD, and DLQI in the total population. *AD* atopic dermatitis, *DLQI* Dermatology Life Quality Index, *EASI* Eczema Area and Severity Index, *SCORAD* SCORing Atopic Dermatitis, *SD* standard deviation

in the last 12 months with an average duration of 23.7 days in patients with at least one flare. The mean (SD) number of routine healthcare visits in the past 12 months was 5.2 (5.2; median 4.0 [IQR 2.0–7.0]) and the estimated rate of routine healthcare visits was 5.2 (95% CI 4.9–5.6), while the mean (SD) number of acute/emergency healthcare visits in the past 12 months was 0.5 (1.6; median 0.0) and the estimated rate of acute/emergency healthcare visits was 0.5 (95% CI 0.4–0.6). Mean (SD) monthly out-of-pocket expenses and extra amount spent as a result of AD were 64.8 (122.6) USD and 47.1 (63.7) USD, respectively, in the total population.

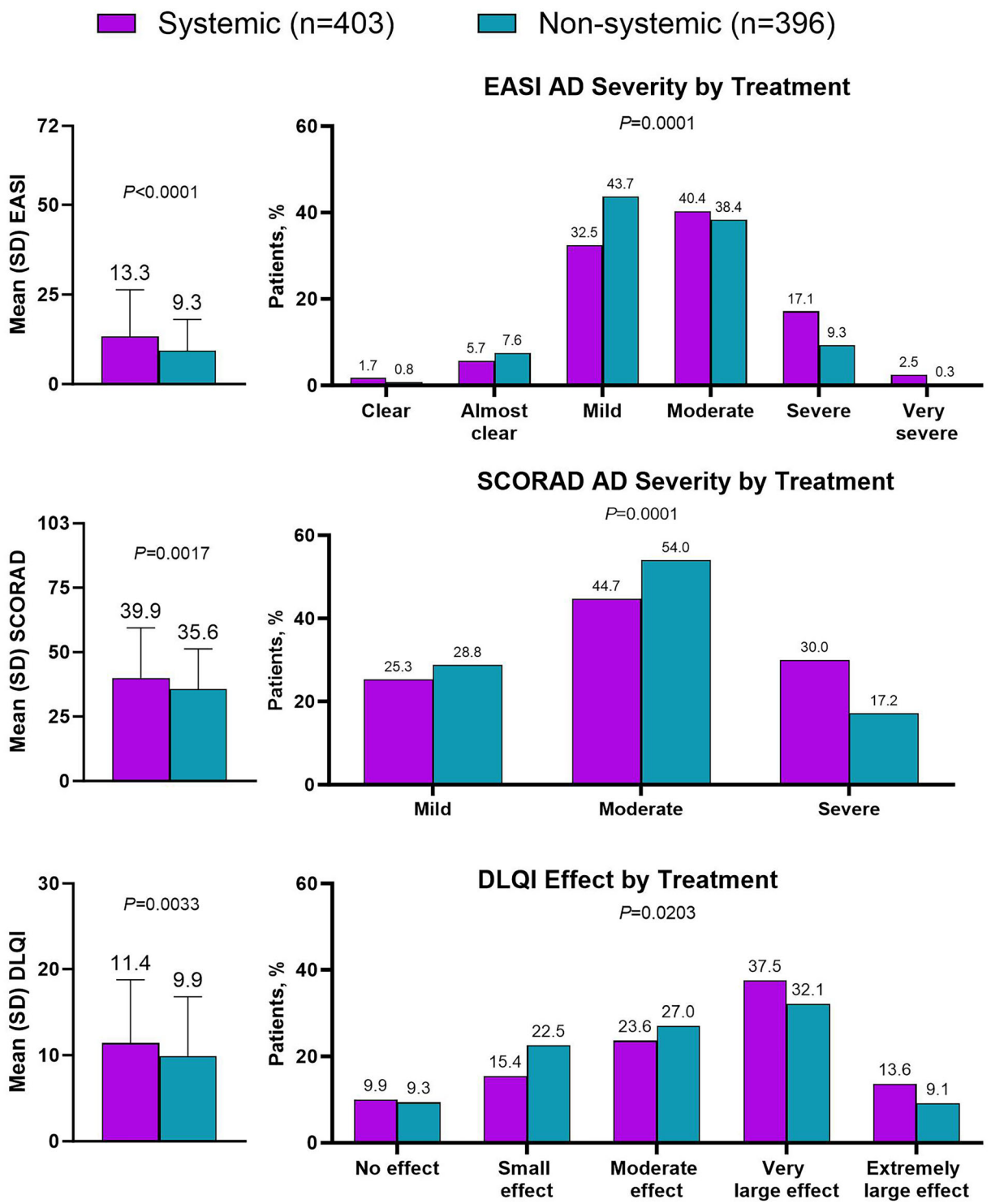

Fig. 3 EASI, SCORAD, and DLQI total scores and severity or impact categories in patients treated with systemic therapies versus non-systemic therapies. *AD* atopic dermatitis, *DLQI* Dermatology Life Quality Index, *EASI* Eczema Area and Severity Index, *SCORAD* SCORing Atopic Dermatitis, *SD* standard deviation

Table 2 Comparison of secondary endpoints between systemic and non-systemic users

	Total population (*n* = 799)	Systemic therapy users (*n* = 403)	Non-systemic therapy users (*n* = 396)	*P* value
WP-NRS				0.1477
Mean (SD)	5.3 (2.7)	5.4 (2.8)	5.2 (2.6)	
Median (IQR)	5.0 (3.0–7.0)	6.0 (3.0–8.0)	5.0 (3.0–7.0)	
WPAI-AD				
Absenteeism, %	*n* = 502	*n* = 265	*n* = 237	
Mean (SD)	8.7 (20.0)	9.8 (21.2)	7.4 (18.5)	0.2106
Median (IQR)	0.0 (0.0–9.1)	0.0 (0.0–10.0)	0.0 (0.0–7.0)	
Presenteeism, %	*n* = 513	*n* = 268	*n* = 245	
Mean (SD)	31.9 (28.1)	33.9 (27.7)	29.6 (28.4)	**0.0384**
Median (IQR)	30.0 (10.0–50.0)	30.0 (10.0–50.0)	20.0 (0.0–50.0)	
Overall work productivity impairment, %	*n* = 502	*n* = 265	*n* = 237	
Mean (SD)	35.1 (29.9)	37.8 (30.2)	32.2 (29.3)	**0.0316**
Median (IQR)	30.0 (10.0–55.0)	34.4 (10.0–60.0)	26.2 (10.0–50.0)	
Activity impairment, %				
Mean (SD)	35.7 (28.3)	38.3 (28.2)	33.1 (28.1)	**0.0055**
Median (IQR)	30.0 (10.0–60.0)	40.0 (10.0–60.0)	30.0 (10.0–50.0)	
Clinical course of AD, *n* (%)	*n* = 792	*n* = 400	*n* = 392	< **0.0001**
Seasonal	193 (24.4)	75 (18.8)	118 (30.1)	
Episodic (moderate)	229 (28.9)	101 (25.3)	128 (32.7)	
Episodic (severe)	71 (9.0)	44 (11.0)	27 (6.9)	
Consistent	57 (7.2)	37 (9.3)	20 (5.1)	
Consistent with flares	242 (30.6)	143 (35.8)	99 (25.3)	
Missing	7	3	4	
Flares, past 12 months, *n* (%)	690 (89.0)	350 (89.3)	340 (88.8)	0.8193
Number of flares, past 12 months	*n* = 775	*n* = 392	*n* = 383	**0.0460**
Mean (SD)	3.8 (4.6)	4.2 (5.2)	3.4 (3.8)	
Median (IQR)	3.0 (1.0–5.0)	3.0 (1.0–5.0)	2.0 (1.0–4.0)	
Estimated flare rate in the past 12 months, mean (95% CI)[a]	3.8 (3.6–4.1)	4.2 (3.8–4.6)	3.4 (3.1–3.8)	**0.0034**

Table 2 continued

	Total population (*n* = 799)	Systemic therapy users (*n* = 403)	Non-systemic therapy users (*n* = 396)	*P* value
Average duration of flares, days	*n* = 689	*n* = 350	*n* = 339	0.4254
Mean (SD)	23.7 (39.9)	24.9 (44.0)	22.5 (35.3)	
Median (IQR)	14.0 (7.0–25.0)	14.0 (7.0–25.0)	14.0 (7.0–28.0)	
Number of routine healthcare visits, past 12 months	*n* = 680	*n* = 347	*n* = 333	< **0.0001**
Mean (SD)	5.2 (5.2)	6.1 (5.7)	4.2 (4.4)	
Median (IQR)	4.0 (2.0–7.0)	5.0 (2.0–9.0)	3.0 (1.0–6.0)	
Estimated routine healthcare visit rate, past 12 months, mean (95% CI)[a]	5.2 (4.9–5.6)	6.1 (5.6–6.7)	4.2 (3.8–4.7)	< **0.0001**
Number of acute/emergency healthcare visits, past 12 months	*n* = 621	*n* = 311	*n* = 310	**0.0002**
Mean (SD)	0.5 (1.6)	0.7 (2.0)	0.3 (1.0)	
Median (IQR)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	
Estimated acute/emergency healthcare visit rate in the past 12 months, mean (95% CI)[a]	0.5 (0.4–0.6)	0.7 (0.5–1.0)	0.3 (0.2–0.4)	**0.0009**
Out-of-pocket expenses due to AD, USD				
Monthly healthcare-related expenses				
Mean (SD)	64.8 (122.6)	76.2 (154.7)	53.2 (75.6)	**0.0029**
Median (IQR)	35.9 (16.2–68.7)	44.8 (21.4–81.7)	32.5 (16.2–64.7)	
Monthly extra amount spent on everyday necessities				
Mean (SD)	47.1 (63.7)	48.3 (61.4)	45.9 (66.0)	0.0619
Median (IQR)	27.8 (10.8–63.0)	32.1 (10.8–66.9)	26.8 (9.4–54.5)	

AD atopic dermatitis, *CI* confidence interval, *IQR* interquartile range, *SD* standard deviation, *WPAI* Work Productivity and Activity Impairment, *USD* United States dollar, *WP-NRS* worst pruritus–numeric rating scale
[a]Estimated using negative binomial distribution

At the time of the visit, the disease and economic burden (as measured by WPAI-AD, number of flares, healthcare visits, and out-of-pocket expenses for monthly healthcare-related expenses) were significantly higher among patients treated with systemic therapy versus patients treated with non-systemic therapy (Table 2).

Although approximately similar proportions of patients from each country (approximately 50%) were receiving systemic therapy by study design, the proportions of patients with moderate-to-severe disease based on EASI

categorization varied greatly, being highest in Egypt (88.0%), Slovakia (70.8%), and South Africa (62.7%) and lowest in Lithuania (25.0%), Poland (28.0%), and Algeria (33.3%; see Table S2 in the Supplementary Material for details). Furthermore, the highest out-of-pocket costs were reported in Latvia, Poland, and South Africa, whereas lowest costs were reported in Egypt, Czech Republic, and Russia (see Table S2 in the Supplementary Material for details).

In the Gulf region (Kuwait and United Arab Emirates; combined n = 109), moderate-to-severe disease was reported by 45.9% of patients. However, despite nearly half of the patients having moderate-to-severe disease, the out-of-pocket expenses ranged from the lowest to the middle third of median values (median monthly costs, 32.6 USD for Kuwait and 54.5 USD for United Arab Emirates; see Table S2 in the Supplementary Material for details).

Additional exploratory analyses of time since AD diagnosis, and EASI, SCORAD, and DLQI scores across seven regions clustered based on geographic locations also demonstrated some variation among regions (see Table S3 in the Supplementary Material for details), although median DLQI and SCORAD values were generally less variable than median EASI and time-since-diagnosis values.

DISCUSSION

This analysis of 799 adults from 15 countries across Eastern Europe, the Middle East, and Africa demonstrated that a considerable clinical, QoL, and economic burden exists among patients with AD regardless of treatment. Overall, 54.1% and 73.0% of patients had moderate-to-severe disease based on EASI and SCORAD, respectively, and 71.5% had moderate to very large effects on QoL. In addition, the 12-month flare rate (mean rate 3.8) and flare duration (mean 23.7 days) remained high, suggesting that disease burden was considerable even though all patients were receiving therapy.

These results are consistent with the real-world global MEASURE-AD study that demonstrated substantial disease burden and inadequately controlled disease among adult and adolescent patients with physician-confirmed moderate-to-severe AD who were either receiving or were eligible for systemic therapy for AD across 28 countries [4]. Similarly, high disease burden has been demonstrated in other real-world AD studies [6–8].

A subgroup analysis by therapy demonstrated that disease burden, QoL impact, work impairment, and economic burden were significantly higher in patients who received systemic therapy versus non-systemic therapy. These findings could suggest that patients with more severe disease were primarily treated with systemic therapies. However, a considerable disease burden also existed among patients treated with non-systemic therapies, demonstrated by high mean EASI, SCORAD, flare rate, DLQI, and WP-NRS scores, suggesting that patients did not have their disease signs and symptoms sufficiently managed at the time of this study regardless of whether they received systemic or non-systemic therapy. These findings raise the question as to why the available therapies were ineffective, especially systemic therapies. The number of available therapies for AD has increased in recent years with the approval of JAK inhibitors and biologics. Although both biologics and JAK inhibitors were available at the time of the study, only 11.3% and 2.5% of patients, respectively, were currently treated with these. Interestingly, pruritus was similar between patients receiving systemic versus non-systemic therapy. Modern therapies, such as JAK inhibitors, have a good effect on pruritus [9], and when these therapies become more available across countries, improvement in patient outcomes is expected. Overall, the number of flares and high disease activity in individual patients can guide physicians to decide whether a change in therapy is needed.

Most patients (92% among those who reported) had at least one routine healthcare visit within the past 12 months. In general, patients treated with systemic therapy (including combination therapy) reported using significantly more healthcare resources than patients treated with non-systemic therapy. Previous studies in the Middle East and Africa have demonstrated higher costs for patients treated with AD therapies versus untreated

patients [10] or patients treated with targeted versus non-targeted therapies [11].

Some regional differences were observed in this study. Although the proportion of patients receiving systemic therapy in each country was similar (approximately 50%), disease severity varied greatly, being highest in Egypt, Slovakia, and South Africa and lowest in Lithuania, Poland, and Algeria. Some of these differences may be related to regional or cultural differences in the perception of AD severity, insurance coverage, healthcare system limitations, and differences in patient selection. Delay in diagnosis due to inaccessibility to expert dermatological services could also contribute to more severe disease. Furthermore, availability of advanced and systemic therapies was not the same across all countries, and some countries did not have biologics or JAK inhibitors available during the time of this study. Out-of-pocket expenses due to AD also varied substantially across regions. Highest median out-of-pocket costs were reported in Latvia, Poland, and South Africa, whereas lowest costs were reported in Egypt, Czech Republic, Russia, and Kuwait. Out-of-pocket cost differences may be explained by differences in reimbursement or government assistance; for example, biological therapy is covered by the ministry of health in Kuwait whereas almost no treatments of any kind are covered by medical insurance in South Africa for the small percentage of people who can afford medical insurance.

This was the first study conducted in some of these regions with a large sample size to allow robust and meaningful assessment of AD management. Other strengths of this study included a multicountry setting and enrollment of patients with AD confirmed by a specialist. Furthermore, inclusion criteria selected patients who were either receiving systemic or non-systemic therapy, including patients who were well treated by topical therapies, allowing comparison between these groups. However, the sample size for some individual treatment options was very small, so it may not be feasible to conduct comparisons with statistically meaningful results between separate systemic and non-systemic treatment options with the current data setting; future studies will be considered for this type of analysis.

At the time of the study, the number of biologic therapies and targeted systemic therapies (e.g., JAK inhibitors) was limited, and the approval/reimbursement status varied across geographic regions. Selection bias may have occurred because of the level of treatment availability and AD management routinely done in clinical practice in the different sites. Also, this was a single-visit cross-sectional study that included patients with a wide variety of treatment statuses (e.g., at the beginning of treatment and $\geq$ 1 year of treatment) so the findings should be interpreted with this limitation in mind. A longitudinal follow-up study in this population would be very helpful to collect continuing information on disease burden and activity as well as healthcare costs over the long term.

CONCLUSION

Findings from this cross-sectional study suggest that patients with AD continue to have substantial disease burden regardless of treatment with systemic therapy or non-systemic therapy. The burden was higher among patients receiving systemic therapies, suggesting that a need for more effective therapies still remains and that patients with AD treated with systemic therapies still need effective disease management, including treatments that improve patients' psychosocial outcomes and reduce the economic burden of AD.

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Data Availability. AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual, and trial-level data (analysis data sets), as well as other information (e.g., protocols, clinical study reports, or analysis plans), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications. These clinical trial data can be requested by any qualified researchers who engage in rigorous, independent, scientific research, and will be provided following review and approval of a research proposal, Statistical Analysis Plan (SAP), and execution of a Data Sharing Agreement (DSA). Data requests can be submitted at any time after approval in the US and Europe and after acceptance of this manuscript for publication. The data will be accessible for 12 months, with possible extensions considered. For more information on the process or to submit a request, visit the following link: https://vivli.org/ourmember/abbvie/ then select "Home".

Declarations

Conflict of Interest. Spyridon Gkalpakiotis has served as a consultant, speaker, or investigator for AbbVie, Celgene, Eli Lilly, Janssen, Leo Pharma, Novartis, Pfizer, Sanofi and UCB. Susanna Kannenberg has received honoraria as a speaker and/or investigator from AbbVie, Adcock Ingram, Boehringer Ingelheim, Pfizer, and Sanofi. Külli Kingo has received fees for serving as an investigator in studies sponsored by AbbVie, Celgene, Merck, Mitsubishi Tanabe Pharma, Novartis, Regeneron Pharmaceuticals, and Sandoz. Hanan Rabea Nada reports no conflicts of interest. Margarita R. Rakhmatulina reports no obvious and potential conflicts of interest associated with the publication of this article. Aleksandra Lesiak is a speaker and/or advisor for AbbVie, Almirall, Bausch Health, Bayer, Eli Lilly, Janssen, Mylan, Novartis, Polpharma, Pfizer, Sandoz, Sanofi, and UCB. Alin C. Nicolescu has served as a speaker, investigator or consultant for AbbVie, Eli Lilly, Janssen, Novartis, Pfizer, Sanofi, Servier, and UCB. Razvigor Darlenski has no conflicts of interest. Alaa Masri, Limei Zhou, Teotonio Albuquerque, and Shereen Hammad are full-time salaried employees of AbbVie and may own stock/options. Iman Almasry has received honorarium fees as an investigator for AbbVie.

Ethical Approval. This study was conducted in compliance with the Declaration of Helsinki, applicable local laws, and regulations. Notifications/submissions to the responsible ethics committees (see Table S1 in the Supplementary Material for details), health institutions, and/or competent authorities were performed as required by applicable local laws and regulations. Prior to enrollment, all patients gave written informed consent.

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