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Long-term psychological outcome of patients with moderate-to-severe atopic dermatitis continuously treated with Dupilumab: Data up to 3 years

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Abstract

Dupilumab effectiveness and safety in treating moderate-to-severe atopic dermatitis (AD) have been demonstrated in open-label studies up to 4 years. Evidence about long-term psychological outcome is lacking. This study evaluates the long-term psychological outcome of moderate-to-severe AD patients continuously treated with Dupilumab up to 3 years. A prospective observational real-life study was conducted at an Italian tertiary centre from January 2019 to September 2022. Measures of disease severity and psychological outcomes were assessed at baseline, after 4, 8, 12, 24 and 36 months. A total of 382 moderate-to-severe AD patients were included. After 36 months, EASI-75 and EASI-90 were achieved by 91.8% and 77.2% of participants. Significant improvement ($p < 0.001$; $\omega 2 = 0.18–0.84$) in objective and patient-reported measures of disease severity and in the psychological condition were observed after 4 months of treatment and maintained up to 36 months. Longitudinal analysis of interactions of demographic and clinical features found subgroups of patients who did not reported psychological improvement over the study period notwithstanding the positive clinical response. Long-term improvement in the psychological outcome of moderate-to-severe AD patients continuously treated with Dupilumab is confirmed up to 3 years, supporting its wide use in this population. Between-subject differences in the psychological outcome irrespective of clinical response observed in this study foster the biopsychosocial approach in the clinical management of these patients.

1 INTRODUCTION

Atopic dermatitis (AD) is a common chronic and relapsing immune-mediated inflammatory skin disease characterized by recurrent eczematous lesions with intense itching, affecting approximately 7%–10% of adults worldwide.1, 2 Moderate-to-severe AD adversely affects physical and mental health and is associated with increased incidence of anxiety, depression and sleep disorders.3, 4 Historically, moderate-to-severe AD management required continuous treatment with systemic therapies to stabilize the disease5; however, the use of systemics were limited by the risk/ benefit ratio associated and by the relevant proportion of non-responsive patients.6 Approval of human monoclonal antibody Dupilumab marked a significant turning point for the treatment of patients with moderate-to-severe AD.7 Dupilumab blocks cytokines IL-4 and IL-13 signalling underlying Type 2 inflammation diseases, including AD.8 Dupilumab-induced rapid improvement in AD signs and symptoms was proved in phase III clinical trials few years ago9 and its long-term effectiveness, over time safety and tolerability have been demonstrated in open-label studies up to 4 years.10, 11 Fast clinical improvement resulting from Dupilumab treatment has been also observed to correspond to rapid patient-reported benefit in itching, sleep disturbances, anxiety, depression and physical and mental health up to 32 weeks.12, 13 There is a lack of evidence about long-term psychological outcome of AD patients continuously treated with Dupilumab. This determines a relevant gap of knowledge, due to the well-known close relationship between patient's psychological condition and generation, aggravation and relapse of a wide range of skin diseases, including AD.14 This study was set up to evaluate clinical response and long-term improvement in the psychological outcome of moderate-to-severe AD patients continuously treated with Dupilumab up to 3 years.

2 METHODS

2.1 Study design, participants and procedures

This is a prospective observational real-life study began in January 2019. Data presented in this study were collected until September 2022 and came from a tertiary referral centre for AD in northern Italy (Dermatology Clinic of Turin University Hospital). Outcome measures were assessed at baseline, after 4 (T1), 8 (T2), 12 (T3), 24 (T4) and 36 (T5) months. Consecutive patients more than 14 years old with a clinical or histological diagnosis of moderate-to-severe AD (EASI ≥ 24 or less in cases with eczema in sensitive areas) non-responsive/ contraindicated to cyclosporine were enrolled and started Dupilumab treatment (300 mg qw/ q2w). Participants were assessed at regular visits for drug administration in a standardized setting (examination room). This study was approved by the local ethical committee of the ‘Città della Salute e della Scienza’ University Hospital in Turin (No. CS2/1359) and participants signed informed consent.

2.2 Outcome measures

AD extent and severity were established by dermatologists through the Eczema Area and Severity Index (EASI).15 EASI score ranges 0–72 and is categorized as follows: 0 = clear, 0.1–1.0 = almost clear, 1.1–7.0 = mild, 7.1–21.0 = moderate, 21.1–50 = severe, 50.1–71 = very

severe. Increases of 75% (EASI-75) and 90% (EASI-90) from baseline score are considered parameters for minimal clinically important difference (MCID). Participants self-assessed AD severity through the Patient-Reported Eczema Measure (POEM)16 and Numerical Rating Scale (0–10) for itching (Itch-NRS) and sleep disorders (Sleep-NRS). POEM score ranges 0–28 and a reduction of 3.4 points from baseline score corresponds to MCID. The impact of AD on the quality of life was self-reported by participants completing the Dermatology Quality of Life Index (DLQI).17 DLQI score ranges 0–30 and is categorized as follows: 0–1 = no effect, 2–5 = small effect; 6–10 = moderate effect; 11–20 = large effect; 21–30 = extremely large effect; a reduction of 4.0 points from baseline score corresponds to MCID. Participants self-assessed physical and mental health through the Short Form Health Survey (SF-36).18 Physical (SF36-PSC) and Mental (SF36-MSC) Summary Components were calculated using the standardized three-step procedure. The scoring algorithm of SF36-PSC and SF36-MSC yields a score with mean = 50 and standard deviation = 10 for the normative population of reference. Anxiety and depression were self-rated through the Hospital Anxiety and Depression Scale (HADS).19 HADS score ranges 0–21 for both subscales, with a score of 11 or above indicating clinical symptoms.

2.3 Statistical analyses

Data were analyzed with SPSS software v. 25.0 for Mac (IBM). Two-sided p-value <0.05 was considered statistically significant, unless otherwise specified ($p < 0.01$). One-way repeated measure analysis of variance (ANOVA) models with the Bonferroni post hoc test to calculate pairwise comparisons were performed to estimate significance and amount of change in outcomes across observation times. Effect-size estimate $\omega 2$ was calculated to correct $\eta 2$ bias and standardize the magnitude of the effects. Omega squared values of 0.01, 0.06 and 0.14 correspond to small, medium and large effect respectively. Two-way and three-way mixed ANOVA models were performed to study group differences over time (within-subject factor), where groups are formed by one or a combination of two between-subject factors (demographics, clinical features). Follow-up tests were performed to explore main effects. Mutual relationships between outcome variables were explored by calculating Pearson's correlation coefficient r. Pearson r values of 0.10, 0.30 and 0.50 indicate small, medium and large effect respectively. Hierarchical multiple linear regression models were run to study the effect of outcome variables, demographics and clinical features on physical and mental health.

3 RESULTS

3.1 Participants characteristics

The sample included 382 participants with moderate-to-severe AD (Table 1). No significant between-group differences in clinical features were found at baseline concerning outcome variables.

3.2 Treatment response across 3 years: Change in outcome variables throughout the study period

EASI-75 and EASI-90 were obtained by the 87.0% and 58.6% of the participants after 4 months and by the 91.8% and 77.2% after 36 months of treatment. Detailed percentages of MCIDs achieved by participants are reported in Table 2. Outcomes showed statistically significant improvement overtime: all specified one-way repeated measures ANOVA models were significant ($p < 0.001$) and the effect sizes ($\omega 2$) were large and ranged from 0.18 to 0.84. Post hoc tests revealed statistically significant improvement from baseline to 4 months, succeeding by substantial stabilization up to 36 months, with very small mostly non-significant fluctuations (Table 2). In general, mean scores of EASI, DLQI, POEM, Itch-NRS and Sleep-NRS changed from baseline scores indicating moderate-to-severe disease with moderate or large effect on life to scores that correspond to no or mild disease with no life impact after 4 months of treatment. HADS scores changed from borderline values at baseline to values indicating the absence of clinical symptoms after 4 months of treatment. SF36 Summary Components (SF36-PSC and SF36-MSC) scores moved from below (baseline) to above (T1) the standardized mean score of 50.

Adverse events (AEs) reported were mainly herpetic eruptions, headache, itchy eye and mostly blepharitis and/or conjunctivitis, that generally persist throughout the treatment. Outcomes did not differ between patients who reported or did not report AEs. However, 13 patients discontinued the treatment due to eye disorders and one due to headache (Table 2).

3.3 Treatment response after 4 months: Psychological outcomes interactions with patients' characteristics

Concerning POEM, significant two-way interaction was found between time and gender ($F = 5.653$, $p = 0.018$, $\eta 2 = 0.022$): females outscored males at baseline ($p = 0.011$), while after 4 months of treatment both genders showed almost equivalent scores.

Concerning SF36-PSC, significant two-way interactions were found between time and gender ($F = 4.757$, $p = 0.028$, $\eta 2 = 0.021$), time and age group ($F = 3.647$, $p = 0.028$, $\eta 2 = 0.033$) and time and age of AD onset ($F = 4.712$, $p = 0.031$, $\eta 2 = 0.021$): males outscored females at baseline ($p = 0.005$), while after 4 months of treatment both genders showed almost equivalent scores; regarding age and age of AD onset, no significant differences were observed between different age groups and groups of AD onset at baseline, while after 4 months of treatment patients over the age of 50 reported worse physical health than those aged 19–30 ($p = 0.001$) and patients with age of AD onset within the first year of age or by age 18 reported better physical health than those with age of AD onset of 19 or above ($p < 0.001$).

Concerning SF36-MSC, significant two-way interactions were found between time and age of AD onset ($F = 16.249$, $p < 0.001$, $\eta2 = 0.070$): no significant differences were observed at baseline, while after 4 months of treatment patients with age of AD onset within the first year of age or by age 18 reported better mental health than those with age of AD onset of 19 or above ($p = 0.009$).

Concerning HADS, significant three-way interactions were found between time, gender and age of AD onset for HADS-A ($F = 6.826$, $p = 0.010$, $\eta2 = 0.027$) and HADS-D ($F = 5.516$, $p = 0.020$, $\eta2 = 0.022$): a significant simple main effect of age of AD onset after 4 months of treatment was found among females ($p = 0.022$) for HADS-A, that is anxiety score was significantly higher ($p = 0.015$) in females with age of AD onset of 19 or above than those with age of AD onset within the first year of age or by age 18; regarding HADS-D, no significant simple two-way interactions of gender and age of AD onset were found at baseline ($p = 0.066$) nor after 4 months of treatment ($p = 0.735$). Similarly, significant three-way interactions were found between time, age group and age of AD onset for HADS-D ($F = 3.559$, $p = 0.030$, $\eta2 = 0.029$) and SF36-MSC ($F = 2.779$, $p = 0.042$, $\eta2 = 0.038$): no significant simple two-way interactions of age group and age of AD onset were found at baseline for HADS-D ($p = 0.450$) and SF36-MSC ($p = 0.725$) nor after 4 months of treatment ($p = 0.317$ and $p = 0.352$ respectively).

One-way repeated measures ANOVA models performed distinguishing outputs according to gender, age group and age of AD onset (i.e. demographics that had shown significant interactions with outcomes in mixed models) revealed that all the subgroups identified obtained significant improvement in the psychological condition with the following exceptions: patients with age of AD onset of 19 or above and aged 30 years or less did not reported a significant improvement in mental health ($p = 0.909$); females with age of AD onset of 19 or above did not reported a significant improvement in depression and anxiety ($p = 0.154$, $p = 0.233$).

3.4 Correlation and regression analysis

Correlations between outcome variables were calculated separately at baseline and 4 months of treatment. At baseline, all psychological outcomes were correlated each other but not with EASI score. After 4 months of treatment, all outcomes correlated each other, including EASI and Itch-NRS scores (Table S3). Hierarchical regression model predicting physical health at 4 months of treatment (M3a) was statistically significant ($F = 8.041$, $p < 0.001$) and accounted for approximately the 36% (adj. $R2 = 0.359$) of the dependent variable with 9 significant predictors (Table S4). The addiction of outcomes at 4 months of treatment to the prediction led to a statistically significant increase in R2 of 0.252 ($F = 11.226$, $p < 0.001$); the further addiction of gender, age group and age of AD onset led to a further statistically significant increase in R2 of 0.048 ($F = 5.293$, $p = 0.002$). Hierarchical regression model predicting mental health at 4 months of treatment (M3b) was statistically significant (F

= 16.225, p < 0.001) and accounted for approximately the 55% (adj. R2 = 0.547) of the dependent variable with 6 significant predictors (Table S4). The addiction of outcomes at 4 months of treatment to the prediction led to a statistically significant increase in R2 of 0.428 (F = 28.00, p < 0.001); the further addiction of gender, age group and age of AD onset led to a further statistically significant increase in R2 of 0.017 (F = 2.6523, p = 0.050).

4 DISCUSSION

Participants in this study showed long term significant improvement in signs and symptoms of AD up to 3 years of continuous treatment with Dupilumab, with reported AEs and rates of discontinuation in line with the documented safety profile of this drug.9-11

The original contribution of this study is that it provided new evidence about the improvement in the psychological condition of patients with moderate-to-severe AD continuously treated with Dupilumab. This result is noteworthy for multiple reasons. First, most of the patients in this study, in line with the literature,1 has developed signs of AD within the first year of age, with symptom burden having always only been partially controlled by systemic therapies until they began Dupilumab treatment, as proven by moderate-to-severe EASI scores showed at baseline, that resulted in a large effect of the disease on life, poor physical and mental health, clinical/ subclinical anxiety and depression, sleep disturbances. Following a marked clinical improvement after long debilitating disease, a relevant betterment in the psychological condition may not be surprising. However, Dupilumab is quickly effective in countering AD signs, generally relieving itching within 4 weeks, and leading to appreciable skin clearance within 16 weeks,10, 20 and then stabilizes the condition, free of signs of the disease, as long as the treatment continues. It has in fact been observed that AD worsens soon in case of Dupilumab discontinuation.21 Bearing in mind the fatigue associated with a chronic therapy, requiring invasive administration twice a month, and the persistent side effects, size and temporal extent of the improvement in the psychological condition associated with Dupilumab treatment observed in this study are truly remarkable, and may well have been contained by the widespread COVID-19 pandemic psychosocial sequelae.22 Beyond that, these results are positively welcomed also because they encourage to deem unlikely the chance of AD relapse fostered by fluctuations or downward adjustment in the psychological condition over time. However, future studies could address the impact of the marked clinical improvement ensured by new resolutive therapies with biologics on a wide range of psychological and behavioural aspects of the person who had suffered for a long time from a chronic childhood-onset disease such as AD. By way of example, symptom remission and the consequent improvement in quality of life and psychological well-being does not ensure the abandonment of unhealthy behaviours and habits (e.g. sedentariness, weight gain and obesity, smoking, alcohol and substances misuse/ abuse) frequently observed among AD patients who expose them to increased risk of recurrence of atopic manifestations and development of multiple medical comorbidities.23, 24

In-depth analysis controlled for EASI score to exclude the lack of clinical response to treatment showed that females reported a more consistent improvement than males as regards perceived AD severity and physical health; patients aged 19–30 reported a greater enhancement in physical health than those younger or older; patients with age of AD onset within the first year of age or by age of 18 reported a more consistent improvement in physical and mental health than those with age of AD onset of 19 or above; females with age of AD onset within the first year of age or by age 18 reported a greater reduction of anxiety and depression than those with age of AD onset of 19 or above. Further separate analysis revealed that patients aged 30 years or less with age of AD onset of 19 or above (approximately 3.1% of the whole sample) did not reported significant improvement in mental health and females with age of AD onset of 19 or above (approximately 8.1% of the whole sample) did not reported significant reduction of anxiety and depression. These results are in line with previous observations19 and suggest that patients under the age of 30, with age of AD onset of 19 or above (i.e. patients who have begun to suffer from AD in adulthood and rather recently), often, but not exclusively, females, might perceive less benefit as regards the psychological status in spite of clinical response to treatment. These patients developed AD in their early adulthood, few years ago, thus they have not grown up with the disease stabilized by systemic therapies, unlike most participants in this study. The rapid and marked switch in clinical condition induced by Dupilumab might have pushed them through a succession of ups and downs which may have made it difficult for them to achieve stability in the psychological adjustment. Correlation and regression analysis in this study found significant associations between demographics, patient-reported measures of symptom burden and objective markers of disease severity. No evidence supports the role of psychosocial factors in mediating or moderating the impact of Dupilumab-induced clinical response on patients' psychological improvement to date. However, recent studies have already documented the complex linkage between demographics, social asset, life events, psychological state, illness history and features, unhealthy behaviours and atopic eczema symptom severity.25, 26 Future studies should investigate more in-depth the relationships between these variables to clarify the underlying biopsychosocial interactions.

Main strengths of this study include sample size, representing the Italian AD population treated with Dupilumab, duration, focus and novel insights on psychological outcome. The main limitation is the absence of control group and/or comparisons with other systemic therapies or novel agents and the lack of in-depth information about participants' psychological history and profile.

5 CONCLUSION

The sustained improvements in objective markers of the disease and in the psychological condition, besides the safety profile Dupilumab demonstrated up to 3 years support its long-term continuous use to treat adults with moderate-to-severe AD. Findings about the interactions between demographic and clinical features and psychological outcome support the adoption of a biopsychosocial perspective in the clinical management of these patients.

AUTHOR CONTRIBUTION

M.M. designed and conducted the study, analyzed and interpreted the data and wrote the manuscript. S.R. supervised the study and critically reviewed the manuscript. L.M. critically reviewed the manuscript. M.O. collected the data. F.G. collected the data. M.B. collected the data. J.T. collected the data. B.S. collected the data. P.Q. supervised the study and critically reviewed the manuscript. P.L. supervised the study and critically reviewed the manuscript. All the authors approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest, financial or others.

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Variable, *n* (%)	*N* = 382
Age group	
≤18	25 (6.5)
19–30	129 (33.8)
31–50	131 (34.3)
51–90	97 (25.4)
Sex	
M	168 (44.0)
F	214 (56.0)
Education	
Primary/ secondary school	88 (23.0)
High school	196 (51.3)
University degree	98 (25.7)
Marital status	
Married/ defacto	182 (47.6)
Single/ divorced/ widowed	200 (52.4)
Current employment	
Paid work	252 (66.0)
Not working	124 (32.5)
Retired	6 (1.6)

Age of AD onset	
Within the first year of age	216 (56.5)
≤18	66 (17.3)
19–30	29 (7.6)
≥31	71 (18.6)
Localization of AD	
Head and neck	6 (1.6)
Upper limbs	3 (0.8)
Lower limbs	5 (1.3)
More than half of the body	137 (35.9)
Diffuse	231 (60.5)
Phototype	
I	12 (3.1)
II	149 (39.0
III	199 (52.1)
IV	22 (5.8)
Hair colour	
Black	32 (8.4)
Brown	319 (83.5)
Blonde	28 (7.3)
Red	3 (0.8)
Eyes colour	
Brown	277 (72.5)
Blue	57 (14.9)
Green	48 (12.6)
Previous treatment	
Topical steroids	375 (98.2)
Topical calcineurin inhibitors	169 (44.2)

Variable, *n* (%)	N = 382
Systemic steroids	360 (94.2)
Cyclosporine	318 (83.2)
Phototherapy	35 (9.2)
Allergies	226 (59.2)
Asthma	86 (22.5)
Rhinoconjunctivitis	65 (17.0)
Alopecia	7 (1.8)
Psychiatric disorder	10 (2.6)
Tobacco consumption	
Non−/Ex-smoker	221 (57.9)
<10 cigarettes/die	70 (18.3)
≥10 cigarettes/die	91 (23.8)
Alcohol consumption	
None	154 (40.3)
Occasionally	201 (52.6)
Habitually	27 (7.1)
BMI category	
<18.5	24 (6.3)
BMI category	
<18.5	24 (6.3)
18.5–24.9	229 (59.9)
25–29.9	99 (25.9)
>30	30 (7.9)

TA B L E 1 Baseline characteristics of the whole sample.

Outcome	YEAR 1			YEAR 2	YEAR 3							
	T1 (4 months)	T2 (8 months)	T3 (12 months)	T4 (24 months)	T5 (36 months)							
	n = 382	*n* = 382	*n* = 311	*n* = 310	*n* = 103							
EASI75	87.0%	85.8%	89.6%	92.6%	91.8%							
EASI90	58.6%	60.1%	74.3%	78.3%	77.2%							
DLQI-mcid	84.1%	90.2%	89.1%	90.1%	92.3%							
POEM-mcid	86.4%	92.1%	90.2%	90.6%	91.3%							
								One-way repeated measure ANOVA - pairwise comparisons (*p*-value)				
	Descriptive statistics, M±SD					*F*	ω^2	B-T1	T1-T2	T2-T3	T3-T4	T4-T5	B-T5
EASI	2.2±2.3	2.3±2.8	2.6±2.8	1.2±1.6	1.5±1.8	194.530*	0.84	<0.001	1.000	1.000	0.025	1.000	<0.001
DLQI	3.6±4.0	2.8±3.3.	3.6±3.7	2.7±3.6	1.9±3.5	65.674*	0.63	<0.001	1.000	1.000	1.000	1.000	<0.001
POEM	5.2±5.2	5.1±5.3	5.1±5.1	4.7±5.3	3.9±4.9	51.115*	0.59	<0.001	1.000	1.000	1.000	1.000	<0.001
Itch-NRS	2.2±2.3	1.9±1.9	2.2±1.9	2.3±2.2	1.6±2.2	90.228*	0.70	<0.001	1.000	1.000	1.000	1.000	<0.001
Sleep-NRS	0.7±1.7	0.4±1.3	0.2±1.4	0.4±1.3	0.2±0.9	61.049*	0.61	<0.001	1.000	1.000	1.000	1.000	<0.001
HADS-A	5.1±3.1	4.5±2.9	4.6±3.2	4.5±4.1	3.8±3.5	13.543*	0.28	0.006	1.000	1.000	1.000	1.000	<0.001
HADS-D	4.1±2.9	4.5±2.9	4.2±3.1	3.5±3.3	3.7±3.3	6.974*	0.18	0.033	1.000	1.000	1.000	1.000	0.013
SF36-PSC	51.4±7.8	53.5±4.3	51.6±5.6	53.9±5.6	53.3±5.6	45.159*	0.81	<0.001	1.000	1.000	1.000	1.000	<0.001
SF36-MSC	51.7±18.8	49.5±12.6	47.3±8.4	49.0±9.6	51.0±5.2	4.037*	0.22	0.013	1.000	1.000	1.000	1.000	<0.001
Adverse event	*n* (%)					Bring to treatment discontinuation, *n* (% of the whole sample)							
IS reaction	5 (1.3)	6 (1.6)	4 (1.3)										
Oral herpes	13 (3.4)	23 (6.0)	15 (4.8)	6 (1.9)	4 (3.9)								
Headache	7 (1.8)	3 (0.8)											1 (0.3)
Hair loss		3 (0.8)	3 (0.9)										
Blef./ Conj.	44 (11.5)	47 (13.3)	37 (11.9)	21 (6.8)	9 (8.7)							13 (3.4)	
Itchy eyes	13 (3.4)	6 (1.6)	4 (1.3)	2 (0.6)	2 (1.9)								
To report													
Ineffec.												12 (3.1)	
Loss of effect.													8 (2.1)
Cancer onset													4 (1.0)
Pregnancy													4 (1.0)
Patient's will													2 (0.5)

TA B L E 2 Effectiveness outcomes, adverse events and reasons for discontinuation of Dupilumab throughout 3 years of treatment.

Abbreviations: Blef./ Conj., Blepharitis or Conjunctivitis; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EASI75 and
EASI90, Improvement of 75% and 90% in the score from baseline; HADS-A, Hospital Anxiety and Depression Scale-Anxiety subscale; HADS-D,
Hospital Anxiety and Depression Scale-Depression subscale; IS reaction, Reaction to the injection site; Itch-NRS, Numerical Rating Scale for
itch; m ± sd, Mean ± standard deviation; mcid, Minimal Clinically Important Difference from baseline; POEM, Patient Oriented Eczema Measure; SF36-MSC, Short Form Health Survey - Mental Health Summary Component; SF36-PSC, Short Form Health Survey - Physical Health Summary Component; Sleep-NRS, Numerical Rating Scale for sleep disorders; ω2, Effect size.*Significant at 0.05 level.