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Impact of the COVID-19 pandemic and lockdown on the clinical response to dupilumab treatment and the psychological status of non-infected atopic patients

Background: Dupilumab is an effective treatment for atopic dermatitis and was found to improve results of clinician- and patient-oriented tests with relevant benefits across multiple domains related to the disease. *Objectives:* To investigate the effects of significant psychological stress on clinician- and patient-oriented tests for severe AD patients treated with dupilumab. Patients were investigated before and during the COVID-19 pandemic and lockdown in a severely affected area. *Materials & Methods:* Forty-five adult patients suffering from severe AD were enrolled. Clinician-oriented (EASI, SCORAD and NRS scores for sleep loss and itching) and patient-oriented tests (DLQI, POEM and HADS) were administered at baseline (T0) and after 16 (T1) and 24 (T2) weeks. The T2 examination took place just before the outbreak of the COVID-19 pandemic. A further examination took place at 32 weeks (T3) during the COVID-19 pandemic and lockdown. *Results:* In comparison to baseline, dupilumab treatment rapidly improved the scores of all tests. After this, the pandemic and lockdown started, and scores of clinician-oriented tests remained almost stable, while patient-oriented scores markedly deteriorated, although they remained better than at baseline. Some personal and social situations seemed to be linked to a worse result. *Conclusion:* Despite dupilumab being effective in inducing and maintaining clinical remission of AD, the COVID-19 pandemic and lockdown significantly impaired patients' perception of the disease, quality of life and anxiety and/or depression. However, this psychological status did not modify the therapeutic response to dupilumab.

Key words: COVID-19, dupilumab, atopic dermatitis

In the last two decades, a close pathogenetic interplay between atopic dermatitis (AD) and the psychological status of patients has been observed [1]. Atopic skin lesions are a significant cause of stress due to intense itching, sleep disturbances, disfigurement and the frequent consequent anxiety, however, depression may be successfully treated with an effective dermatological treatment [2]. Conversely, a worsening of skin lesions is observed in the presence of significant stress, probably mediated by psycho-neuro-immunological and endocrinological mechanisms [1, 3].

Dupilumab, a fully human monoclonal antibody that binds specifically to the shared α-chain subunit of interleukin (IL)-4 and IL-13 receptors (IL-4R-α) is an effective treatment for improving skin lesions of moderate and severe AD [4] and itching and was found to concurrently improve sleep loss, anxiety, depression, quality of life and daily activities and productivity at work and school [5]. However, these improvements were observed in normal living conditions and the effect of situations of extreme psychological stress is unknown. Such a situation occurred during the COVID pandemic and lockdown, especially in areas with very high incidence and mortality rates (+300% compared to the average mortality rate of previous years), such as Lombardy in March and April 2020.

At the time of the outbreak of the pandemic, we were conducting a study of the efficacy and psychological impact of dupilumab therapy in patients with severe AD and therefore, we had the unique chance to measure the course of the therapy before and during the COVID pandemic and lockdown, and evaluate which environmental variables could most influence its performance.

Materials and methods

This was an observational longitudinal study. We enrolled adult patients suffering from severe AD (Eczema Area and Severity Index [EASI] ≥24) who started a treatment cycle with dupilumab [6, 7] in September and October 2019 at

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the Dermatologic Department of ASST Spedali Civili di Brescia, Italy.
Exclusion criteria were pregnancy or breast feeding, other inflammatory skin diseases, contraindications to dupilumab, congenital or acquired immunodeficiency syndrome, concomitant immune-suppressive therapies, and inability to understand and sign the informed consent form.
Dupilumab treatment was performed according to established methods with standard dosages (a 300-mg subcutaneous injection every other week after an initial dose of 600 mg) in all patients and was never discontinued during the COVID pandemic.
At baseline (T0), the main personal features of patients were registered (ethnicity, age, gender, duration of AD, family history of AD, any concomitant atopic/allergic diseases and occupation [employee, self-employed or other, *e.g.* housewife, student, retired or unemployed]) and patients underwent a full medical examination.
Two additional medical examinations were planned after 16 (T1) and 24 (T2) weeks. Given that at the time of T2, the COVID pandemic was starting in our area, we decided to extend the study with an additional examination after 32 weeks (T3). In the interval between T2 and T3, patients experienced the worst period of the COVID 19 pandemic and the most stringent lockdown conditions in Italy. During this period, patients were told to contact, as soon as possible, the dermatology department if any alarming signs (*e.g.* fever, cough, dyspnoea, anosmia, ageusia or diarrhoea) developed.
At all timepoints, clinician-oriented (EASI, SCORAD [*Scoring of AD*]) [8] and patient-oriented scores (DLQI [*Dermatology Life Quality Index*] [9], POEM [*Patient Oriented Eczema Measure*] [10], HADS [*Hospital Anxiety and Depression Scale*] [11]) were assessed; patients were also asked to quantify their itch and sleep loss on a 10-point numerical rating scale (NRS). In addition, we recorded the tolerability of the drug and any adverse reactions to treatment. At T3, the validated Italian version of Perceived Stress Scale (PSS) [12] was used to measure patients' perception of stress during the COVID pandemic and their psychological distress. In addition, several features of daily life during the lockdown were asked, regarding: occupational status (working on-site, working from home, or no longer working); number of people living at home (and their relationship to the patient); number and type of pets; type (house or apartment), location (urban or countryside), and size (more or less than 100 square meters [sqm]) of dwelling; and whether there is a garden and/or balcony.
All patients provided signed written informed consent prior to any study procedure. The study followed the principles outlined in the Declaration of Helsinki and was approved by the Local Ethics Committee (Spedali Civili di Brescia, Protocol Number: 4203).

Statistical analysis

The database was formatted using Microsoft-Excel ™ software and subsequently imported from IBM-SPSS ™ ver. 25.0.1.
For the statistical analysis, the continuously expressed variables were subjected to the Kolmogorov-Smirnov test to evaluate their normal distribution. Continuous variables were compared using the most appropriate parametric and non-parametric tests (Mann-Whitney U-test, Kruskal-Wallis test and Wilcoxon test), while the associations between categorical variables were tested using the Chi-squared test. Any correlation between PSS values and POEM, DLQI and HADS variation was evaluated by Pearson correlation and linear regression.
All results were analysed with an α significance level of 5%.

Results

We enrolled 45 adult Caucasian patients (29 males and 16 females). The median age was 40 years (range: 19-78 years) and the median duration of AD was 12 years (range: 2-47 years). Seventeen (37.8%) patients had a family history of AD and 31 (68.9%) had other concomitant atopic/ allergic manifestations, *i.e.* asthma ($n = 18$, 40%) and allergic rhinitis and/or conjunctivitis ($n = 23$, 51.1%).
Adverse effects attributable to dupilumab were minor and appeared before the COVID outbreak: naso-pharyngitis and/or conjunctivitis (6/45 at T1 and 2/45 at T2) and injection site reactions (3/45 at T1). At T3, no patient had or reported COVID-related symptoms and/or contact with COVID-positive cases.
At baseline (T0), scores for EASI, SCORAD, NRS of itching, NRS of sleep loss, DLQI, POEM and HADS were particularly low in all patients. All T1, T2 and T3 scores showed a statistically significant improvement ($p \leq 0.001$ for all) in comparison to baseline scores (*table 1*).
In order to evaluate the effect of the COVID-19 pandemic and lockdown on objective and subjective scores, we compared the differences of variation (Δ) of each score before (T1-T2) and during the COVID-19 pandemic (T2-T3) (*table 2*). The T2-T3 values for EASI, SCORAD and NRS for sleep loss and itching remained roughly stable compared to T1-T2 values (*table 2*), whereas there was a significant difference for all patient-oriented scores (POEM, DLQI and HADS) between T1-T2 Δ and T2-T3 Δ (*table 2*).
To evaluate whether environmental factors affecting daily life during quarantine (type of occupation and residence, working activity and family members) played a role in the worsening of patient-oriented scores, subjects were divided into two groups. In Group 1 ($n = 29$, 64.4%), we included patients for whom at least two patient-oriented scores had decreased at T2-T3, while for patients ($n = 16$, 35.6%) of Group 2, at least two of these scores remained unchanged or improved during the COVID-19 pandemic. The comparison revealed statistically significant differences with a greater rate for subjects working at home in Group 2 (58.3% vs. 16.0%, $p = 0.008$) and those who had lost their jobs in Group 1 (48.0% vs. 8.4%, $p = 0.018$) (*table 3*). The rate for patients who remained at home, in a house larger than 100 sqm, during lockdown was significantly higher in Group 2 (68.7% vs. 34.5%, $p = 0.027$) (*table 3*). The presence of elderly persons or children within the family and pets, and the type and location of residence and/or the availability of open-air spaces did not influence the results.
The Kruskal-Wallis test was used to evaluate the variation of patient-oriented scores (POEM, DLQI and HADS) in Group 1 based on working activity and size of house, how-

Table 1. Clinician-oriented scores, NRS for itching and sleep loss and patient-oriented scores at baseline (T0), Week 16 (T1), Week 24 (T2) and Week 32 (T3).

	T0	T1	T2	T3	*p* (T0-T1)	*p* (T0-T2)	*p* (T0-T3)
EASI	27.9 (25.2;30.3)	6.6 (3.4;9.1)	4.4 (2.6;8.0)	4.1 (2.9;7.5)	≤0.001*	≤0.001*	≤0.001*
SCORAD	62.0 (55.5;71.4)	19.5 (15.1;29.4)	18.0 (13.3;23.2)	15.5 (11.0;22.8)	≤0.001*	≤0.001*	≤0.001*
NRS sleep loss	7.0 (3.5;8.0)	0.0 (0.0;2.0)	0.0 (0.0;1.5)	0.0 (0.0;2.0)	≤0.001*	≤0.001*	≤0.001*
NRS itching	8.0 (5.5;9.0)	2.0 (1.0;3.5)	2.0 (1.0;3.0)	2.0 (1.0;4.0)	≤0.001*	≤0.001*	≤0.001*
POEM	17.0 (11.5;22.0)	4.0 (2.0;7.5)	4.0 (1.5;7.0)	8.0 (3.5;13.5)	≤0.001*	≤0.001*	≤0.001*
DLQI	13.0 (7.5;17.5)	1.0 (0.0;6.5)	1.0 (0.0;4.0)	3.0 (1.0;8.5)	≤0.001*	≤0.001*	≤0.001*
HADS	14.0 (8.5;19.0)	5.0 (2.5;9.0)	4.0 (2.0;8.5)	9.0 (3.5;15.0)	≤0.001*	≤0.001*	≤0.001*

*Results are given as median and IQR. * denotes a statistically significant difference.*

Table 2. Comparison of variation of clinician-oriented scores, NRS for itching and sleep loss and patient-oriented scores between T1-T2 and T2-T3.

	Δ (T1-T2)	Δ (T2-T3)	*p*
EASI	-12.1 (-56.2;0.0)	0.0 (-22.8;26.6)	0.101
SCORAD	-11.3 (-23.6;-0.36)	-9.2 (-25.8;10.4)	0.426
NRS sleep	0.0 (0.0;0.0)	0.0 (0.0;1.0)	0.818
NRS itch	0.0 (-1.0;0.5)	0.0 (-1.0;2.0)	0.100
POEM	0.0 (-1.0;1.0)	2.0 (-0.5;6.0)	0.015*
DLQI	0.0 (-1.5;0.0)	1.0 (0.0;3.0)	≤0.001*
HADS	0.0 (-2.5;0.0)	3.0 (0.0;7.5)	≤0.001*

*Results are given as median and IQR. * denotes a statistically significant difference.*

Table 3. The effect of aspects of daily life during quarantine in Group 1 (patients with lower scores at T2-T3, based on at least two patient-oriented scales) and Group 2 (patients with unchanged or improved scores).

	Group 1 (*n* = 29)	Group 2 (*n* = 16)	*p*
Type of occupation			
Employee	21 (72.4%)	9 (56.3%)	0.133
Self employed	4 (13.8%)	3 (18.7%)	0.661
Other (housewife, student, retired, unemployed)	4 (13.8%)	4 (25.0%)	0.347
Working activity	25 (86.2%)	12 (75.0%)	0.347
On-site	9 (36.0%)	4 (33.3%)	0.874
At home	4 (16.0%)	7 (58.3%)	0.008*
Laid off	12 (48.0%)	1 (8.4%)	0.018*
Family members			
Elderly and/or children	14 (48.3%)	7 (43.7%)	0.771
Pets	11 (37.9%)	9 (56.3%)	0.236
House			
House /apartment	11 (37.9%) / 18 (62.1%)	7 (43.7%) / 9 (56.3%)	0.703
<100 sqm / ≥100 sqm	19 (65.5%) / 10 (34.5%)	5 (31.3%) / 11 (68.7%)	0.027*
Garden and/or balcony / no outdoor spaces	14 (48.3%) / 15 (51.7%)	10 (62.5%) / 6 (37.5%)	0.360
Urban space / countryside	23 (79.3%) / 6 (20.7%)	13 (81.3%) / 3 (18.7%)	0.876

**denotes a statistically significant difference between the groups. Sqm: square meters.*

ever, the results were not statistically significant, although the difference in median score values was higher in patients who were temporarily laid off and who spent quarantine in a house smaller than 100 sqm (*table 4*).

Regarding the analysis based on PSS, values were higher in Group 1 (median: 19.0; IQR: 10.0;23.0) compared to Group 2 (median value: 15.5; IQR: 6.3;25.0), however, this difference was not statistically significance ($p = 0.740$). A positive correlation was seen between PSS and POEM ($R = 0.053$, $p = 0.731$) and DLQI ($R = 0.189$, $p = 0.231$) values. PSS values also positively correlated with HADS variation, reaching statistical significance ($R = 0.411$, $p = 0.005$). Linear regression revealed that PSS values were significantly associated with HADS variation

Table 4. Variation of patient-oriented scores (POEM, DLQI and HADS) in Group 1 based on working activity and size of house.

	POEM variation	DLQI variation	HADS variation
Working activity	$p = 0.786$	$p = 0.182$	$p = 0.096$
On-site	6.0 (2.0;13.0)	3.0 (1.0;8.0)	6.0 (6.0;12.0)
At home	4.0 (2.0;9.0)	1.0 (0.5;4.0)	3.0 (1.0;7.0)
Laid off	7.0 (2.0;11.0)	4.0 (2.0;6.0)	7.0 (0.5;9.0)
Size of house	p = 0.963	p = 0.944	p = 0.153
<100 sqm	4.0 (2.0;11.5)	3.0 (1.0;6.0)	7.0 (5.0;10.0)
≥100 sqm	4.0 (2.0;10.0)	2.5 (1.0;4.3)	4.0 (1.8;7.3)

Results are given as median and IQR; Sqm: square meters.

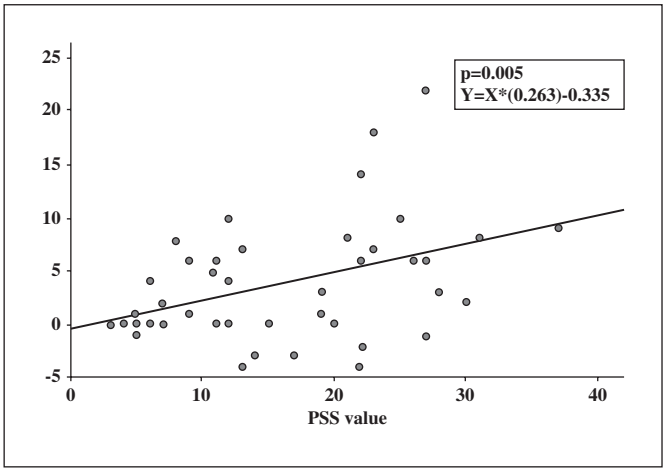

Figure 1. Atopic dermatitis: correlation between HADS variation and PSS values in all patients.

in all patients [$Y_{HADS} = X_{PSS}*(0.263)-0.335$; $p = 0.005$] (*figure 1*).

Discussion

In the present study, we had the unique chance to compare the effects of dupilumab therapy on clinician- and patient-oriented scores in severe AD patients living in an usual social/healthcare situation. Moreover, patients experienced deep psychological stress because of the severity of the COVID-19 pandemic and the rigorous lockdown in a town with a 300% increase in mortality, in comparison to average mortality of the previous five years [13], and an estimated contagion rate of 20% [14].

Dupilumab was always well tolerated and very effective, and all clinician- and patient-oriented scores remained low at a significant level compared to baseline throughout the entire study (*table 1*). However, while clinician-oriented tests and NRS scores for sleep loss and itching did not change significantly before and during the pandemic, scores for patient-oriented tests were significantly lower during the pandemic (T2-T3) in comparison to before the pandemic itself (T1-T2).

We wondered whether some aspects of patients' daily lives during quarantine had an effect on the variation of these scores. When comparing patients with (Group 1) or without (Group 2) at least two low patient-oriented scores (POEM, DLQI and HADS) during the COVID-19 pandemic, we noticed that scores were lowest in subjects who had concerns of financial insecurity because they had lost their job in comparison to subjects who kept working (at the office or at home) or those living in a house smaller than 100 sqm. In addition, we found that values for the stress perception (PSS test) were higher in patients of Group 1, and values positively correlated with the variation of patient-oriented scores, however, statistical significance was found only for HADS variation (*figure 1*).

Therefore, these findings suggest that, despite the stability of the condition, the COVID-19 pandemic significantly impacted on patients' psychological condition and on their quality of life.

Unlike the trend for patient-oriented scores and the PSS test, the positive effects of dupilumab on all clinician-oriented scores for disease severity, itching and sleep remained stable while patients remained on continuous therapy during the COVID-19 pandemic and lockdown. Therefore, efficacy and tolerability of dupilumab remained high irrespective of the heavy burden of stress that patients experienced (*table 1*). This "real-life" finding apparently contrasts with the results of previous experimental studies in which atopic dermatitis was found to be aggravated by psychological stressors through effects on cutaneous immune and endocrinological pathways [15-18]. A possible explanation for this discrepancy is that stress, even at a high level, does not reduce the therapeutic efficacy of dupilumab.

To our knowledge, this is the first study to analyse patients with atopic dermatitis before and during the pandemic period and lockdown. However, it has some limitations,

including the lack of assessment of psychological status of AD patients at baseline and the limited number of patients enrolled [4, 19, 20].

In conclusion, our findings suggest that dupilumab remains effective in reducing AD severity even if patients are experiencing a very stressful situation that significantly impairs their perception of the disease and negatively impacts their quality of life, with anxiety and depression. ■

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