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Effects of lockdown on health of patients with severe atopic dermatitis treated with dupilumab

Dear Editor,

Use of dupilumab as treatment for severe adult atopic dermatitis (AD) increased over time since its introduction in September 2018, due to its established efficacy. AD is one of the most common chronic inflammatory skin disease affecting up to 14.3% of adults, with 63.3% of these cases first appearing before 18 years of age.[1] Patients' disease burden is important with high rate of discomfort, less confidence in daily life activities and psycho-social distress. The introduction of dupilumab changed the natural history of this disease, drastically improving AD manifestations and therefore quality of life.[2]

In 2020, the COVID-19 epidemics started spreading in Italy, leading the Government to establish urgent and strict restriction measures in avoid to contain the spread of the infection. Lombardy region has been the first epicentre of the health crisis starting mid-February. Shortly after, the virus spread to other regions with a relevant number of infected patients, forcing a general lockdown from March 9 to May 4. During this time span, individuals were allowed to leave the household only for grocery shopping and proven basic necessities, while only first-need shops and services were allowed to operate. In the hospital setting, only urgent visits were performed, and our ward was only available to dispense dupilumab and assess severe cases.

We describe our experience in the Dermatology Unit of our hospital in Milan, observing how lockdown period influenced clinical and psychological aspects of patient with severe AD in therapy with dupilumab.

The cohort was made up of 106 out of 252 adult patients with severe AD in treatment with dupilumab in our centre (Table 1).

Inclusion criteria were a follow up visit during or shortly after the lockdown period (March 1–June 15) and correct adherence to the therapy for at least 1 year.

After clinical evaluation, we calculated Eczema Area and Severity Index (EASI) and asked each patient to complete a survey including Numeric Rating Scale (NRS) for the evaluation of itch, NRS for evaluation of sleep quality, Dermatology Life Quality Index (DLQI) and Patient-Oriented Eczema Measure (POEM); then we also assessed disease's psychological impact on quality of life and Hospital Anxiety and Depression Scale (HADS) for depression (HADS-D) and anxiety (HADS-A).

We decided to exclude patients under therapy for <1 year because we felt that clinical improvement and perception of better quality of life could be over-felt by the patient during this phase, inducing a bias.

We performed a retrospective analysis comparing surveys collected during the lockdown time against baseline from the same

Table 1 Data analysis

Scores	Mean predupilumab	Mean Prelockdown	Mean Postlockdown	Variation %	*P*-value
EASI	31.7	3.89	3.01	−23%	<0.005
HADS-D	7	2.92	3.60	23%	<0.005
HADS-A	7.8	3.38	3.51	3.8%	*
ITCH NRS	8.8	2.69	2.65	−0%	*
SLEEP NRS	6.9	0.63	0.62	−0%	*
DLQI	16.2	3.10	3.18	2.6%	*
POEM	21.5	6.93	6.42	−7.4%	*

Prelockdown: December 1 – February 29.
Postlockdown: March 1 – June 15.
*Other changes in variables considered were not statistically relevant.

patient, seeking for any significant difference. Results are show in Table 1.

We used paired t student test to statistically validate the results ($\alpha = 1\%$ $t\alpha/_2 \pm 2.623$).

According to the literature, all collected parameters should have improved at the same time to different degrees until 52th weeks of treatment with dupilumab.[3] Instead, HADS-D score declined by 23% with statistical significance ($P < 0.0005$), even though the disease severity decreased, with a calculated EASI improving on average by 23% ($P < 0.0005$) over the considered period.

In contrast, we observed a diffused decline of patients 'psychological status (HADS-D) during the lockdown phase, with scores worsening in comparison with those from the prelockdown. They generally felt depressed, grieve, slowed down and tired in the daily routine and more frequently in a bad mood. This worsening of HADS-D is unexpected.

In effect, our data show a paradoxical effect: a marked AD clinical improvement as assessed by means of EASI with a decline in the psychological scores. This may be explained by the confinement in the households with less recreational activities, fear of contagion and loss of positive vision for the future.

Our observations are not isolated, as other published studies reported an increase in anxiety during lockdown in patients in treatment with biologic therapies for other conditions.[4]

Conflicts of interest

None declared.

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LETTERS TO THE EDITOR

Immediate hypersensitivity reaction to ixekizumab in a patient with psoriasis

Editor

Ixekizumab is a humanized immunoglobulin G monoclonal antibody targeting the IL-17A, and labelled to treat moderate-to-severe plaque psoriasis.

Benign skin reactions are a common adverse event when using ixekizumab. In a meta-analysis of phase III studies, ixekizumab appears to have had the highest rate of skin reactions among all anti-IL-17 and IL–12-IL-23 agents,[1] affecting approximately 25–30% of treated patients.[2] A severe type III hypersensitivity resulting in serum sickness-like reaction has been described.[3] Our literature review showed no other cases of severe allergy.

We report a case of type 1 hypersensitivity to ixekizumab in a 44-year-old woman with no significant medical history and specifically no history of allergies. She had been treated for a severe psoriasis with local treatments, PUVA therapy and apremilast, which showed poor results. This led to treatment with ixekizumab: 160 mg on the first injection followed by 80mg every two weeks. The first four ixekizumab injections were well-tolerated, leading to a PASI 100. Fifteen minutes after the fifth injection, she felt tingling in her fingers, arms, and axillary and inguinal creases, followed minutes later by an itchy urticarial eruption. One hour after taking two pills of desloratadine, the eruption disappeared. Thus, the patient presented a grade I reaction on the Ring and Messmer scale. We recommended that she discontinues ixekizumab. Etanercept was introduced with no side-effect. An allergological workup was performed four months later, under etanercept. The skin prick test (SPT) with a pure solution of ixekizumab was positive with an 8 mm papule. The intradermal test (IDT) diluted in a saline concentration of 10^{-2} was positive too, with a 12mm papule (Fig. 1). Prick tests were also run with a nasal solution ProRhinel® and an anti-cough syrup FLUISEDAL® both containing polysorbate 80 as excipient, just as in the ixekizumab solution. These were negative. We concluded that the patient had a type 1 immediate allergy to ixekizumab itself. We contraindicated this molecule.

We thereby report a rare case of true allergy to ixekizumab proven by positive SPT.

Polysorbate could be allergenic or irritant, and it seems to be the cause in most cases of non-severe cutaneous reactions.[4] It could also

