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**COVID-19: Important updates and developments**
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# Impact of COVID-19 on patients with atopic dermatitis ☆

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**Abstract** Data on the tolerability and response to biologic therapies for type 2 immune disorders in the context of coronavirus disease 2019 (COVID-19) are currently lacking. Our survey aimed at assessing the adherence of patients to dupilumab therapy and the risk of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. A total of 80 patients with atopic dermatitis treated with dupilumab completed a web-based survey. Of the 80 patients, 7 discontinued dupilumab owing to concerns and difficulties related to COVID-19. Our sample was highly susceptible to viral infection owing to the frequency of risk factors including living in high SARS-CoV-2 burden areas, such as in Northern Italy; having comorbidities, such as asthma, diabetes, and cardiovascular disease; and being of advanced age. Older patients in our sample are particularly exposed to the risk of COVID-19–related cytokine storm, triggered by excessive interleukin-4 production and type 2 immune response. One patient contracted SARS-CoV-2 infection without the progression of COVID-19 despite continuing scheduled dupilumab treatment. Because evidence on the appropriate management of biologic therapy in the setting of COVID-19 is lacking, the collection of clinical data from patients in treatment with dupilumab is a valuable addition to current clinical practice. Our survey provides a contribution to the understanding of the tolerability and response to dupilumab during COVID-19 and suggests a feasible and effective approach to patients being treated with biologics even when social distancing is required.


## Introduction

Dupilumab, an anti–interleukin (IL)-4/IL-13 human monoclonal antibody, is the first biologic treatment approved by the European Medicines Agency and the Food and Drug Administration in 2017 for the treatment of moderate-to-severe atopic dermatitis (AD) in patients who are candidates for systemic therapy.[1-3] The drug is a powerful suppressor of type 2 cytokine production, being an inhibitor of IL-4/IL-13 receptors.[4] It is also currently being evaluated for its potential application in other allergic diseases, including asthma[5] and chronic rhinosinusitis with nasal polyps.[6]

Owing to its high rate of contagion and the shocking rate of spread, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has raised worldwide concern about the use of biologic therapies during the pandemic.[7] There has been a lack of knowledge about the possible inter-

☆ How does COVID-19 impact atopic dermatitis patients in dupilumab therapy? An investigative online survey

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ference of immune-modulating drugs with the coronavirus disease 2019 (COVID-19)–associated cytokine storm and their potential role in promoting viral replication and lethality.[8] The many restrictions on interpersonal contacts, especially in medical practice, have created a significant problem for the management and follow-up of patients receiving biologics.

The use of biologic drugs selectively targeting type 2 inflammatory mediators may be considered safe in the current epidemic setting. The European Task Force on Atopic Dermatitis recently stated that "targeted treatment selectively interfering with type-2 inflammation such as dupilumab is not considered to increase the risk for viral infections."[9] This is contrary to traditional immunosuppressive therapies, including cyclosporine and methotrexate, that should be avoided in the COVID-19 era.[9] According to the evidence gathered to date from clinical studies, biologic immunomodulating therapies should not be discontinued, in spite of COVID-19 infectivity[10]; however, the role of these therapies during the current pandemic is yet to be clarified, and additional real-life data must be collected.[11]

Compounding the problem are the current restrictions placed on health care facilities. Hospitals are considered a possible source of infection,;therefore,access and the number of procedures performed has been reduced dramatically. It can be a challenge for physicians to promote therapeutic continuity in patients suffering from chronic disorders and at the same time to minimize hospital exposure. A strategy to address the issue is teledermatology.

The aim of our study was to investigate the patient's perspective on dupilumab treatment in the setting of COVID-19, using a purposely designed online survey. The questionnaire addressed the effects of COVID-19 on the management of treatment. Each patient was provided information about adherence to dupilumab therapy and activity of AD, as to improvement, worsening, or stability. These data allowed us to assess the quality of life of patients and their tolerability to dupilumab during the COVID-19 epidemic.

## Materials and methods

A total of 80 Italian patients aged ≥18 years, with moderate-to-severe AD, and treated with dupilumab were included in the survey. Median duration of treatment was 6 months (range: 1–18 months). All subjects, irrespective of survey completion, received monthly (T1 = February, T2 = March, T3 = April) follow-up phone calls to collect patient-reported outcomes regarding itch numeric rating scale (NRS), sleep NRS, and severity NRS.

All patients receiving dupilumab during the lockdown period, February 3, 2020 to May 29, 2020, were approached in the course of a routine teleconsultation and asked to complete the survey. Patients who provided consent were given a link to the online survey.

Each patient was given the same online questionnaire (Google forms; Google LLC, Menlo Park, CA) in the Italian language. All answers were self-reported. No personal data, such as name, e-mail address, or internet protocol address, were requested to preserve the patient's anonymity. No patient received remuneration for participating in the study.

The questionnaire investigated the following aspects: demographic characteristics including age, sex, and residence; clinical characteristics including personal history focused on risk factors for COVID-19; recent flu-like symptoms; and management of dupilumab therapy during national lockdown.

### *Statistical analysis*

Data were reviewed for potential confounders before any statistical analysis was performed. Descriptive statistics were performed. Quantitative variables were expressed as median (range) or mean ± standard deviation, as appropriate. Qualitative variables were described as frequency and percentage. Patient-reported outcomes were expressed using an NRS collected at monthly intervals (T1 = February, T2= March, T3 = April). Outcomes at T1 and T3 were compared by using the Wilcoxon signed-rank test, a nonparametric test for comparing two related samples. Measurements at T1-T2-T3 were compared by using the Friedman test, a nonparametric statistical test that detects eventual differences across serial measurements. A value of $P < .05$ was considered statistically significant.

## Results

We enrolled 80 patients in the study, 39 men(48.8%) and 41 women(51.2%), with a median age of 31.5 years (18-89 years). Of the 80 enrolled patients, 59 completed the online questionnaire, with a response rate of 73.8%. Our sample was representative of both higher-risk and lower-risk regions in Italy, because 12 patients (15%) lived in such high-risk areas as Veneto and Lombardy, and 56 patients lived in the lower-risk area of Lazio. Of the patients who completed the online questionnaire, 11 reported direct exposure to the COVID-19 infection, after contact with acquaintances, relatives, and coworkers in 6, 3, and 2 cases testing positive, respectively. A total of 40 patients (50.0%) had at least one comorbidity associated with increased susceptibility to SARS-CoV-2. Of responding patients, 36 (45%) were diagnosed with asthma, which is associated with up to 35% to 45% cases of AD as well as with increased susceptibility to viral respiratory infection.[12] Six patients (7.5%) had cardiovascular disease, one had diabetes mellitus, and one had a history of pneumonia. Only eight patients (10%) received the seasonal flu vaccine.

We also monitored adherence to the therapeutic protocol. A total of 73 patients continued receiving dupilumab at the standard dosing every 2 weeks. All these patients had a positive response to treatment and did not suffer from any compli-

**Table 1** Patient-reported outcomes of 80 patients affected by atopic dermatitis treated with dupilumab during the COVID-19 pandemic

| Patient-reported outcomes | | |
|---|---|---|
| NRS pruritus median [range] | | |
| - T1 | 2 [0–8] | $P = .62189$* |
| -T2 | 2 [0–8] | ns |
| -T3 | 2 [0–7] | |
| NRS sleep median [range] | | |
| -T1 | 0 [0–9] | $P = .72253$* |
| -T2 | 0 [0–7] | ns |
| -T3 | 0 [0–6] | |
| NRS severity median [range] | | |
| -T1 | 2.5 [0–6] | $P = .18731$* |
| -T2 | 2.5 [0–7] | ns |
| -T3 | 2.5 [0–5] | |

COVID-19, coronavirus disease 2019; NRS, numeric rating scale (1-10); ns, not significant.

* Comparison among T1-T2-T3 measurements was performed by using the Friedman test with repeated measures (T1 = February 2020, T2 = March 2020, T3 = April 2020).

cation or concomitant disease. A few patients (7) interrupted treatment, five owing to personal concerns, one owing to difficulty in retrieving the drug, and one following recommendations of a physician. In the course of monthly telephone contacts, all patients were asked to report the intensity of pruritus, of sleep disturbances related to AD, and the perceived severity of cutaneous lesions.

Patient-reported outcomes were measured using NRS at monthly intervals (T1= February, T2= March, T3 = April) to highlight trends associated to a change in disease (Table 1). No statistically significant differences between outcomes at T1 and T3 was demonstrated with the Wilcoxon signed-rank test for pruritus score ($P = .4654$), sleep symptoms ($P = .88076$), or lesion severity score ($P = .19706$). No statistically significant differences across T1-T2-T3 were demonstrated with the Friedman test for repeated measures for pruritus score ($P = .62189$), sleep symptoms ($P = .72253$), and lesion severity score ($P = .18731$).

Only seven (8.8%) patients in our sample complained of flu-like symptoms, despite their unfavorable risk profile characterized by the following: comorbidities associated with increased susceptibility to viral respiratory infection, travel within high-risk areas, or potential exposure to SARS-CoV-2. The symptoms resolved within 1 week in five patients, and in two patients symptoms lasted either up to 2 weeks or >2 weeks. The latter two cases were associated with a high fever >37.5°C. In addition, three patients (3.8%) were subjected to quarantine, and three underwent nasopharyngeal swab for virus RNA, with one positive result. Patient characteristics and examination variables are described in Table 2.

**Table 2** Personal characteristics and clinical features of 80 patients affected by atopic dermatitis treated with dupilumab during the COVID-19 pandemic

| Patient characteristics | | |
|---|---|---|
| Response rate, n (%) | 59 | 73.8% |
| Sex, n (%) | | |
| Men | 39 | 48.8% |
| Women | 41 | 51.2% |
| Age, median [range] | 31.5 [18–89] y | |
| EASI (last assessment before lockdown), mean ± SD | 9.10 ± 11.27 | |
| High SARS-CoV-2 burden geographical setting, n (%) | 12 | 15% |
| Comorbidities, n (%) | | |
| Asthma and airway disease | 36 | 45% |
| Cardiometabolic disorders | 3 | 3.8% |
| both | 1 | 1.2% |
| TOTAL | 40 | 50% |
| Treatment interruption, n (%) | | |
| Personal decision | 5 | 6.3% |
| Difficulty consulting physician | 1 | 1.2% |
| Difficulty drug supplies | 1 | 1.2% |
| TOTAL | 7 | 8.8% |
| Flu-like symptoms, n (%) | 7 | 8.8% |
| Fever >37.5°C, n (%) | 2 | 2.5% |
| Symptom duration, n (%) | | |
| <1 wk | 5 | 6.3% |
| 7-14 d | 1 | 1.2% |
| >14 d | 1 | 1.2% |
| Positive SARS-CoV-2 PCR, n (%) | 1 | 1.2% |

COVID-19, coronavirus disease 2019; EASI, eczema area and severity index; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, standard deviation.

## Discussion

Dupilumab is a human IgG monoclonal antibody directed against the $\alpha$ subunit of IL-4R. Its binding restricts signaling induced by IL-4 and IL-13, key cytokines of type 2 inflammation, and fundamental players in the pathogenesis of AD. These cytokines are able to downregulate the expression of epidermal barrier genes contributing to epidermal barrier disruption. IL-4 and IL-13 are known to enhance the release of proinflammatory cytokines, histamine, and other potent mediators of inflammation.[13] Finally, activation of the IL-4/IL-13 receptor and histamine receptors on nerve fibers is responsible for the enhanced sensation of pruritus due to hyperactivation of dermal sensory nervous fibers.[14]

The immune pathogenesis of SARS-CoV-2 recognizes several proinflammatory cytokines—such as IL-6, TNF, IL-1beta, and IL-17—each a known contributor to the COVID-19–related cytokine storm, the ultimate cause of multiorgan failure and death in most patients with COVID-19.[15] Interferon production seems to be downregulated in COVID-19

infection, as a mechanism to delay clearance of the virus from the organism.[16]

Hypothetically, the use of biologics that are highly selective for a single cytokine, such as anti-IL-6 tocilizumab or anti IL-1beta anakinra, could constitute a potential therapeutic option in the treatment of COVID-19.[17] Recent evidence in the literature has highlighted that dupilumab does not worsen the clinical condition in subjects with SARS-CoV-2 infection, possibly owing to the neutralization of specific inflammatory mediators rather than to broad immunosuppression.[18]

A recent study investigated the potential role of dupilumab in positively modulating the inflammatory response in advanced COVID-19 infection. IL-4 is hypothesized to be a major driver of the cytokine storm, especially in the older population, and of the fatal hemophagocytic lymphohistiocytosis syndrome. IL-4 is universally known for its role in inflammatory lung diseases including asthma and some endotypes of chronic obstructive pulmonary disease.[19] In addition, patients with AD frequently have asthma and rhinosinusitis. Dupilumab was recently approved for the treatment of severe type 2 asthma that cannot be controlled with previous-line drugs. In this setting, dupilumab could protect patients not only from the risk of an asthmatic exacerbation, but it could also reduce the susceptibility to severe respiratory infection.[20]

These hypotheses are highly attractive, because they could support the use of already approved agents in the management of COVID-19, for which specific treatment is not yet available. Such proposed mechanisms of action partially explain the safety profile of dupilumab and the success of therapy during the current pandemic. Knowledge about the role of dupilumab in individuals exposed to COVID-19 remains largely lacking.[21,22]

Finally, there are no data on patients taking dupilumab who received the newly available COVID-19 vaccines. According to a recent study assessing tetanus and meningococcal vaccines after treatment with dupilumab, responses indicated that non-live vaccines were apparently unaffected and vaccination was not associated with adverse clinical events.[23] We hypothesize that COVID-19 vaccines could similarly prove safe and immunogenic in adults with moderate-to-severe AD treated with dupilumab; however, these speculations require future testing in placebo-controlled trials.

During our observation period, more than 240,000 cases of SARS-CoV-2 infection had been diagnosed in Italy, accounting for more than 34,000 deaths.[24] Despite the overall high risk of infection, 73 patients (91.2 %) continued treatment with dupilumab at regular intervals. Patients in our sample were exposed to risk factors for infection and complications, including living in high-risk areas (15%), male sex (48.8%), age >65 years, and respiratory (45%) and cardiometabolic (3.8%) comorbidities. Only seven patients in our study complained of flu-like symptoms, with no patient requiring hospitalization. The duration of symptoms was 1 week in five patients, as well as 2 and 3 weeks in the remaining two patients. One of these patients tested positive for SARS-CoV-2 RNA. This patient continued regular administration of dupilumab during the febrile phase of COVID-19 and showed no worsening of AD.

Even if withdrawal from therapy is commonly suggested in these cases, our decision to continue treatment was supported by the targeted anti-type 2 anti-inflammatory action of dupilumab. Continuation of therapy allowed all our patients to remain free from skin signs of active AD throughout the course of the lockdown period. Finally, we recommend that clinicians introduce surveys in their current medical practice to strengthen patient reliance on the attending physicians and to improve compliance with treatment, especially when personal interactions between patient and specialist are significantly limited.

## Conclusions

In line with published studies on the tolerability of dupilumab in the COVID-19 era, our survey agrees with the sustained use of this drug in such setting.[25] The purpose of our study was to support the safety of dupilumab in a heterogenous population sample, including patients having significant comorbidities and being elderly.

Additional reports together with more robust clinical data are required to elucidate the role of dupilumab and of other monoclonal antibodies in the setting of SARS-CoV-2 infection.[11] Such studies as proposed should encourage the use of biologics without reservation in the COVID-19 era and provide physicians with the solid evidence needed to guide their decisions in daily practice.

## Conflict of interest

The authors declare no conflict of interest.

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