

Funding sources: none.

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DOI: 10.1111/jdv.16525

## Safety of dupilumab in severe atopic dermatitis and infection of Covid-19: two case reports

### Editor

Dupilumab is a fully human monoclonal antibody against the alpha subunit of interleukin (IL)-4 receptor that blocks signalling from both IL-4 and IL-13, which are key type 2 cytokines in the pathophysiology of atopic dermatitis (AD).<sup>1</sup> It shows good efficacy with a rapid response and good safety with few side-effects.<sup>2–8</sup> In a paper of Deleuran *et al.*,<sup>9</sup> the authors showed long-term safety and efficacy of dupilumab; they reported viral upper respiratory tract infection, cough and influenza in about 2% of patients. The European Task Force on Atopic Dermatitis in a recent paper<sup>10</sup> stated that dupilumab didn't increase the risk for viral infections and might thus be preferred compared to conventional systemic immunosuppressive treatments in a situation such as the COVID-19 pandemic. However, this theoretical

advantage is not supported by robust clinical data and they recommended all doctors treating AD patients to remain vigilant and updated. We reported two patients with AD and COVID-19 infection in therapy with dupilumab for severe AD. The first patient is a 40-year-old man affected by AD since his early childhood. Due to his severe AD in November 2019, he started subcutaneous injections treated with dupilumab 300 mg every two weeks after a loading dose of 600 mg. Serum examination prior to the beginning of the treatment revealed high levels of immunoglobulin E (IgE) (2152 international unit (IU)/millilitre) and lactate dehydrogenase (LDH 516 unit/L). The Eczema Area and Severity Index (EASI) was 24, while the Dermatology Life Quality Index (DLQI) was 18. After 1 month, the EASI and DLQI were slightly decreased (5 and 8, respectively) and the same trend was reached by IgE (1776 IU/mL) and LDH (400 unit/L). During the third month of therapy, the patient and his father showed symptoms of COVID-19 infection. The patient developed a mild form, while his father died of interstitial pneumonia during hospitalization. The infectivologist decided to continue with dupilumab for our patient and administered acetaminophen obtaining a regular course without complications. The second patient is a 56-year-old woman affected by AD since early childhood. The patient underwent treatment with cyclosporine for 5 months in 2015 without improvement; so, in the last five years, she took prednisone continuously. In October 2019, she was admitted to our outpatient clinic for the persistence of AD despite therapy with prednisone. The patient began treatment with dupilumab in November 2019. At the baseline, serum examination revealed high levels of IgE (560 IU/mL) and normal LDH. The EASI was 28, while the DLQI was 18. After 1 month, EASI and DLQI were slightly decreased (5 and 8, respectively) and IgE was 400 IU/mL. During the fourth month of therapy, the patient and her husband showed symptoms of COVID-19 infection. They were both hospitalized, and her husband died of interstitial pneumonia. Despite the finding of interstitial pneumonia also in our patient, the infectivologist decided to continue therapy with dupilumab and to start therapy with darunavir/cobicistat and hydroxychloroquine. In addition, antibiotic coverage (ceftriaxone) was associated. The patient did not need oxygen therapy due to good respiratory exchange over the time. After 10 days, they obtained a progressive improvement of the clinical picture and the inflammatory indexes without complications or AD flares. We here reported only two cases of patients affected by COVID-19 infection in treatment with dupilumab for severe AD. In our Dermatology Department in Milan, geographic area with a high incidence of COVID-19 infection, we collected 245 patients in therapy with dupilumab and only 2 (0.82%) developed COVID-19 infection. Of these 2 patients, none had complications or abnormal course of the infectious disease. So, based on our experience, we can confirm that dupilumab is an effective and safe therapy for patients with severe AD also in cases of severe infections.

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DOI: 10.1111/jdv.16527

## SARS-CoV-2 infection presenting as a febrile rash

Dear Editor,

The World Health Organization (WHO) has declared that Coronavirus disease 2019 (Covid-19) is a public health emergency of international concern as it continues to spread worldwide.<sup>1</sup>

After a median incubation period of 4 days, fever and cough are the two most common manifestations of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.<sup>2</sup> Physicians

worldwide are facing this new disease for which little is known about the full spectrum of its clinical features. For instance, some patients with Covid-19 associated cutaneous manifestation have been reported, but there is a lack of iconographic and histological documentation.<sup>3–9</sup> Herein, we describe a febrile rash as the only clinical manifestation of SARS-CoV-2 infection in a patient free from pulmonary symptoms.

On March the 7th this year, a 39-year-old Caucasian male with no relevant medical history presented to the emergency department with a fever of 39°C, along with a concomitant skin rash that had appeared the same day. This rash was characterized by erythematous and oedematous non-pruritic annular fixed plaques involving the upper limbs, chest, neck, abdomen and palms, sparing the face and mucous membranes (Fig. 1a–e). Importantly, the patient declared having taken no medication in the days and weeks before the onset of symptoms. His vitals were normal, and he had no signs of upper respiratory tract or pulmonary infection.

The patient promptly reported to the physician that he had been in contact 5 days earlier with a family member, who was afterwards tested positive for SARS-CoV-2. Quantitative reverse-transcriptase–polymerase-chain-reaction (qRT-PCR) assay performed on both nasopharyngeal swab and sputum sample revealed the presence of SARS-CoV-2 RNA. The search for other respiratory viruses, such as influenza A and B viruses, rhinovirus, and common coronaviruses was negative, as was the blood culture. Blood count, electrolytes, C-reactive protein and anti-DNA antibodies were normal too. The histological examination of the skin showed non-specific changes, compatible with viral exanthemata: predominantly superficial perivascular infiltrate of lymphocytes without eosinophils, papillary dermal oedema, subtle epidermal spongiosis, mild lymphocyte exocytosis, lichenoid and vacuolar interface dermatitis with occasional dyskeratotic keratinocytes in the basal layer (Fig. 1f). No virally-induced cytopathic alterations or intranuclear inclusions were present. Direct immunofluorescence was negative.

Despite normal chest radiograph on admission, a chest CT scan showed bilateral and peripheral ground-glass and consolidative pulmonary opacities, highly suggestive of SARS-CoV-2 infection.<sup>10</sup>

On March the 8th, the patient started oral hydroxychloroquine sulfate 200 mg three times per day for 10 days with a daily monitoring of SARS-Cov-2 qRT-PCR on nasopharyngeal swab. No pulmonary symptoms developed. On March the 14th, the rash fully recovered and laboratory tests for SARS-CoV-2 qRT-PCR became negative on March the 20th.

Our case report provides two important facts that need highlighting. Firstly, Covid-19 disease can present with a distinctive rash, which is histologically similar but clinically different to classic viral exanthemata. Indeed, the annular, polycyclic and circinate appearance of the skin lesions differed from classic paraviral rashes in adults, as did the papules on the palms. In addition, unlike viral infection-associated urticaria, the plaques were both fixed and non-pruritic. Secondly, a febrile rash may be the only clinical