Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

Dupilumab maintenance therapy in an asthmatic patient with coronavirus disease 2019 pneumonia

Dear Editor,

Dupilumab is a human monoclonal antibody against the alfa subunit of interleukin (IL)-4 receptor that regulates type 2 inflammation by inhibiting signaling from IL-4 and IL-13. Dupilumab is widely used as an important biologic agent to control severe condition of asthma, eosinophilic chronic rhinosinusitis, and atopic dermatitis. In the pandemic of severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) and its associated respiratory disease, coronavirus disease 2019 (COVID-19), very little is known about the safety of dupilumab use, which may modulate immune response to COVID-19, during stable conditions as well as continuous use after onset of COVID-19. Here, we present a case who continued dupilumab maintenance therapy before and during COVID-19 and recovered from COVID-19 pneumonia safely without exacerbation of asthma.

A 57-year old man with severe atopic asthma (total serum IgE 750 IU/μL with sensitization to house dust mite and *Aspergillus*), obesity (BMI 44 kg/m^2), diabetes, hypertension, and obstructive sleep apnea was tested using PCR because of close contact with his colleague who developed COVID-19. The clinical course is summarized in Figure 1. He was asymptomatic, but diagnosed as COVID-19 (day 1). He was admitted to the hospital for close monitoring on day 3, but had a fever (38.3 °C) and oral favipiravir was started on day 6. No respiratory symptoms had been reported until he rapidly developed dyspnea and hypoxemia and nasal oxygen therapy was started on day 11. On day 12, chest computed tomography (CT) showed bilateral peripheral-dominant ground glass opacity (GGO) and consolidation (Fig. 2A), and because he had several risk factors for severe COVID-19 including obesity and diabetes, he was transferred to intensive care unit at our hospital and received oxygen therapy *via* face mask (5–6 L/min).

At the transfer (day 12), there were no signs of any exacerbation of asthma. In addition to regular inhalation of *relvar ellipta*® 200 μg/*day*, inhaled ciclesonide 800 μg/*day* was started, which has been suggested for anti-viral effect in small case series.[1] Moreover, intravenous administration of dexamethasone 6.6 mg/day and heparin was started. On day 14, favipiravir was switched to remdesivir. He was gradually recovered, a negative PCR for SARS-CoV-2 was confirmed on day 27, oxygen therapy was discontinued on day 28. Follow-up chest CT was performed on day 31. Bilateral GGO was resolved and partially converted to consolidation (Fig. 2B). He was discharged on day 34.

He was a never smoker and diagnosed as asthma at early 40s with higher blood eosinophil (10–20% of total white blood cells). He had been treated with *relvar ellipta*® 200 μg/*day* and mepolizumab for two years, but developed pruritus cutaneus while asthma control was maintained. Then, mepolizumab was switched to dupilumab 2 month before the diagnosis of COVID-19 in the other hospital, and asthma was further well-controlled, blood eosinophil was decreased from 6% to 3% of total white blood cells (from 450/μL to 161/μL), and pruritus cutaneus was resolved. After the diagnosis of COVID-19, he continued administration of dupilumab just before hospital admission (day 3) and during the stay in the hospital (day 17 and 31) based on the recommendation for the use of biologics in the COVID-19 pandemic.[2] Consequently, asthma was kept stable, and quantity of viral load from nasal swab assessed with PCR was consistently decreased from on day 15, 20, to day 27. Blood eosinophil was decreased and kept low (0.1% of total white blood cells) during the systemic corticosteroid treatment, and then returned to the same level as before the COVID-19 (3% of total white blood cells, 143/μL) after discontinuation of the systemic corticosteroid treatment.

Dupilumab is an essential biologic agent for severe type of asthma, eosinophilic chronic rhinosinusitis, and atopic dermatitis. As well as other biologics, there is a concern whether dupilumab can be used safely in the era of COVID-19 pandemic. One of the concerns may stem from its potential modulation of angiotensin-converting enzyme 2 (ACE2) expression. In initial infection of SARS-Cov-2, the spike protein of inhaled virus binds to ACE2 located on lung epithelium membrane. Then, the virus is incorporated into the host epithelium such as alveolar type-2 epithelial cells. This process depends on cellular serine protease, termed transmembrane protease serine 2 (TMPRSS2). Peters *et al.* investigated gene expressions in sputum cells of asthmatic patients and showed that up-regulations of ACE2 and TMPRSS2 are associated with male sex, African American race, and history of diabetes mellitus, which are well known risk factors for poor outcomes of COVID-19.[3] They also showed that high dose of inhaled corticosteroid is related to lower expression of ACE2 and TMPRSS2.[4] Meanwhile, Kimura *et al.* showed that IL-13 down-regulates ACE2 expression and up-regulates TMPRSS2 in bronchial epithelial cells from atopic patients and patients with asthma.[5] Therefore, it is possible that blocking of IL-13 pathways by dupilumab may increase ACE2 and decrease TMPRSS2 expression. However, because both ACE2 and TMPRSS2 are required for SARS-CoV-2 entry to the host epithelium, net effect of blocking IL-13 on the susceptibility to SARS-CoV-2 in atopic patients remain unknown.

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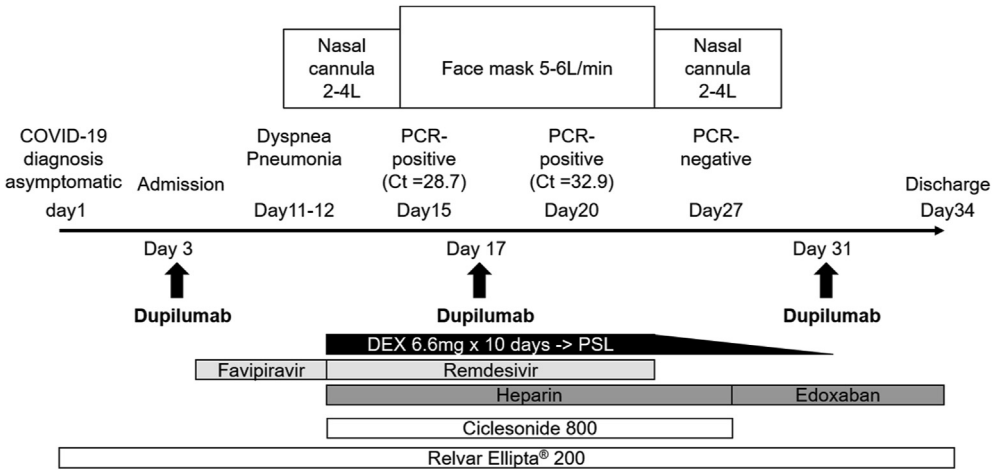

Fig. 1. Clinical course of COVID-19. DEX, dexamethasone; PSL, prednisolone.

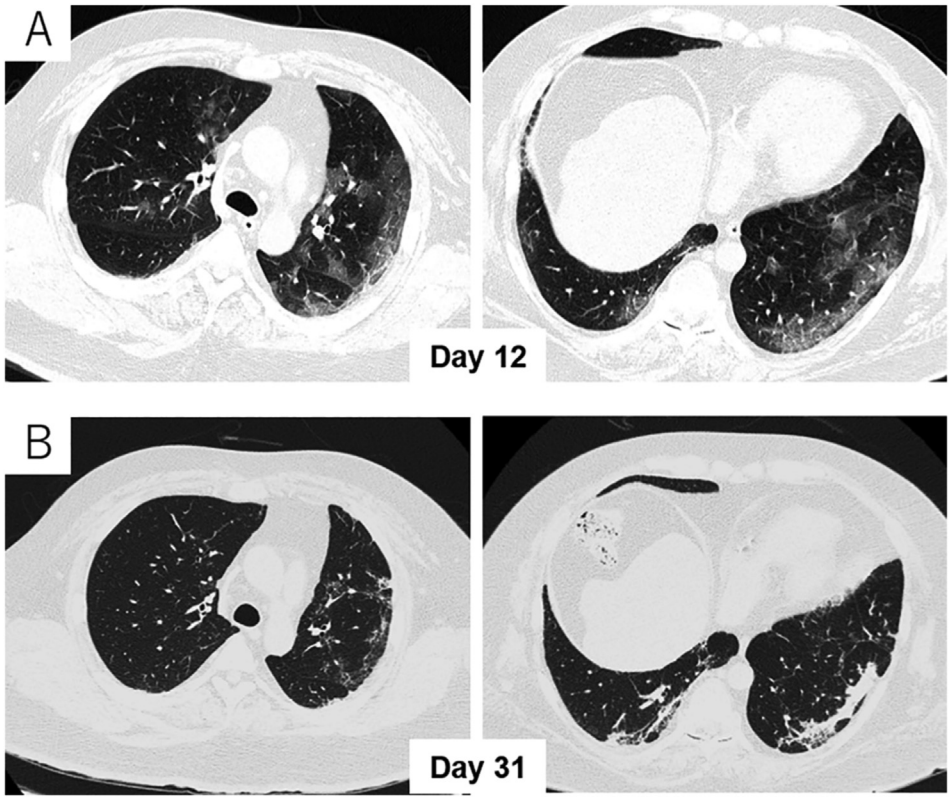

Fig. 2. Abnormal shadows on chest computed tomography. **(A)** Bilateral peripheral-dominant ground glass opacity (GGO) were found on day 12 from COVID-19 diagnosis. **(B)** GGO in the upper regions of lungs were resolved, whereas GGO in the lower regions of lungs was partially resolved and the remaining was converted to consolidation.

As far as we can say, there is no report that indicates the harmful effects *via* dupilumab continuation. Forster-Ruhrmann *et al.* presented a case treated with dupilumab for chronic rhinosinusitis with nasal polyps and asthma, who developed COVID-19 but was completely relieved 2 weeks after the diagnosis of COVID-19.[6] Ferrucci *et al.* also reported two cases with severe atopic dermatitis treated with dupilumab, who developed COVID-19 but showed good recovery.[7] The present asthma case treated with a combination of inhaled corticosteroid/long-acting beta 2 agonist and dupilumab also showed clinical complete recovery from the COVID-19. Collectively, these cases confirm the safety of dupilumab during the active phase of COVID-19 pneumonia.

In the present case, the negative conversion of SARS-CoV-2 PCR was confirmed on day 27, which seems relatively longer than a reported virus shedding time (median [interquartile range] 19 [15–26] days for asymptomatic patients and 14 [9–22] days for symptomatic patients).[8] This is consistent with a case of asthma exacerbation with COVID-19 pneumonia who was treated with methylprednisolone (but not with dupilumab), and required 25 days for the viral clearance.[9] Although a recent randomized trial showed that 10-day dexamethasone treatment reduced the mortality in COVID-19 patients,[10] whether systemic corticosteroid could delay the viral clearance in COVID-19 should be further investigated.

In conclusion, this case report supports the recommendation that the regular uses of biologics including dupilumab should be continued in the pandemic era of SARS-CoV-2[2] and even after development of COVID-19. Further evidence is needed to establish clinical influences of dupilumab on ACE2 and TMPRSS2 expression as well as viral clearance *in vivo* in asthmatic patients.

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Conflict of interest

HM received honoraria from Sanofi outside the submitted work. SH reports grants from Teijin Pharma, outside the submitted work. The rest of the authors have no conflict of interest.

Naoya Tanabe [a], Hisako Matsumoto [a,*], Satoshi Hamada [b], Isao Ito [a], Toyohiro Hirai [a]

[a] *Department of Respiratory Medicine, Graduate School of Medicine, Kyoto University, Kyoto, Japan*
[b] *Department of Advanced Medicine for Respiratory Failure, Graduate School of Medicine, Kyoto University, Kyoto, Japan*

* Corresponding author. Department of Respiratory Medicine, Graduate School of Medicine, Kyoto University, 54 Shogoin Kawahara-cho, Sakyo-ku, Kyoto 606-8507, Japan.
E-mail address: hmatsumo@kuhp.kyoto-u.ac.jp (H. Matsumoto).

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