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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COVID-19 in a patient with severe chronic rhinosinusitis with nasal polyps during therapy with dupilumab

To the Editor:

mAbs (biologics) such as dupilumab, a fully human mAb blocking IL-4 and IL-13 signaling, started recently to be successfully used also for the treatment of severe forms of chronic rhinosinusitis with nasal polyps (CRSwNP).[1] Currently, no data are available on whether the therapy with dupilumab influences the risk of infection with the coronavirus (severe acute respiratory disease coronavirus 2 [SARS-CoV-2]) or whether it modulates the course of coronavirus disease 2019 (COVID-19).

Here, we report a case of a 53-year-old female patient (body mass index, 23.5) treated with dupilumab for uncontrolled severe CRSwNP, who developed COVID-19. Twenty years ago, the patient consulted her physician because of rhinitis, which was consecutively diagnosed as CRSwNP. At that time, she also developed asthma, and in 2005, reported respiratory symptoms following intake of 2 different nonsteroidal anti-inflammatory drugs. No further diagnostic tests were performed. Despite the administration of oral prednisolone 3 times a year, the regrowing nasal polyps had to be surgically removed in 2012, 2016, and 2019. She was receiving prednisolone because of recurrent documented nasal polyps extending beyond the middle nasal passage on both sides (Davos score 4 NP, a sum of both sides). The last course of prednisolone was administered in January 2020. In February 2020, the patient was admitted to our outpatient department for possible alternative treatment and was offered therapy with dupilumab for uncontrolled CRSwNP. Also, she was administered mometasone furoate 400 μg/d, fluticasone/salmeterol 250/50 μg 2 inhalations orally twice a day, 12 hours apart, and salbutamol when needed. The following set of clinical tests used in our clinic as a standard to characterize the patients with CRSwNP was applied:

- Rhinological parameters: Nasal endoscopy Davos score—score 1: NP in middle meatus only; score 2: NP beyond middle meatus; score 3: NP not blocking the nose completely; score 4: NP completely obstructing the nose; a sum of both nasal sides.
- Pulmonary parameters: The Asthma Control Test (ACT) score, with ACT score 20 or more as controlled asthma, ACT score less than 20 as uncontrolled asthma,[2] and FEV_1 and forced vital capacity (FVC) values of spirometric measurements.
- Validated rhinological questionnaires: CRS Symptoms Score 0: no symptoms; 1: mild symptoms; 2: moderate symptoms; 3: severe symptoms[1]; 22-item Sino-Nasal Outcome Test (SNOT-22) with 22 questions, each scored 0 to 5 (total score range, 0-110), with higher scores representing worse quality of life.[3]

At presentation, the pulmonary parameters of the patient were FEV_1/FVC ratio 62%; FEV_1 57%; ACT score 16 (see Table I). Dupilumab (300 mg) was administered on February 24, 2020, in the outpatient ward of the Department of Otorhinolaryngology. The subcutaneous injections with dupilumab were continued on March 8 and 30, 2020, by self-application. Smell impairment, runny nose, and postnasal drip disappeared within 2 weeks from the therapy onset, and the nasal congestion kept improving. The SNOT-22 score decreased from 38 to 8. Between 11 and 15 March, the patient went on a trip with her husband (Table II). On March 14, she reported a return of anosmia while her husband (50 years old, body mass index, 31.6) developed fever, cough, and shortness of breath. Two days later, the patient, too, developed a fever and later cough. The SNOT-22 score increased to 24. On March 16, based on a viral PCR test, the patient and her husband were diagnosed with COVID-19 and were quarantined at home for 2 weeks. The patient continued the treatment with dupilumab by self-injection. Two weeks after the COVID-19 diagnosis, the patient and her husband were entirely relieved from the COVID-19 symptoms. The administration of dupilumab continued at home on March 22, 2020. During the telephone interview on March 30, 2020, the patient reported complete control of nasal polyp symptoms, normosmia, and a low SNOT-22 score.

To summarize, our patient with CRSwNP treated with dupilumab had an unexpectedly light course of COVID-19 (Table II). A few possible reasons might explain that. The first reason for the observed clinical course of COVID-19 in our patient could be that ongoing therapy with dupilumab already after a short time controlled the CRSwNP symptoms by reducing local inflammation and improving nasal respiration. Improvement in sinonasal function could be essential for the initial combating of COVID-19. Before therapy with dupilumab, our patient had poorly controlled asthma. Already after the second injection, she shifted into controlled asthma. Similarly, her nasal symptoms (eg, nasal congestion) improved, positively affecting the upper respiratory tract. The second reason for the light course of COVID-19 might be the recently described negative association between an increased number of eosinophils and the viral load.[4] Such an increase was indeed seen in our patient (see Table E1 in this article's Online Repository at www.jacionline.org), corroborating the observations made during clinical trials with dupilumab.[5] The third possible reason for the uneventful COVID-19 could be that the initial viral load of SARS-CoV-2 was rather low upon infection, and the disease course was not associated with the dupilumab treatment.

Finally, the direct positive effect of dupilumab on COVID-19 cannot be excluded, because it modulates immunity by affecting the T_H2-type immune responses. It is tempting to speculate that this type of modulation might be beneficial to combat COVID-19, which is supported by higher levels of IL-4 associating with a fatal disease.[6] However, our patient received dupilumab for only a short period before infection, while observations made during clinical trials indicated that the full effect of dupilumab on the immune system occurs later.[1]

The continuation of dupilumab treatment during the infection with SARS-CoV-2 is in agreement with our own clinical experience and with the current recommendations of the German Society for Allergology and Clinical Immunology[7] about the continuation of the biologics treatment for severe CRSwNP. Interruption of therapy could lead to the progression of rhinosinusitis, expansion of polyp formation, and worsening of common comorbidities such as asthma. That, in turn, could negatively impact the course of COVID-19 and increase the spread of the virus by coughing. Also, many patients would have to be put back on therapy with systemic glucocorticosteroids if the biologic treatment were discontinued, which could have an undesirable effect on the immune defense against COVID-19. In the case of our patient, systemic glucocorticosteroids were administered just until before

TABLE I. Rhinologic and pulmonary parameters before and during therapy with dupilumab: Symptoms during and after COVID-19

	Timeline					
Parameter	**February 24, 2020 Dupilumab injection 300 mg SC**	**March 8, 2020 Dupilumab injection 300 mg SC**	**March 14, 2020 to March 22, 2020 COVID-19 symptoms**	**March 22, 2020 Dupilumab injection 300 mg SC**	**March 30, 2020 Additional telephone consultation**	**April 22, 2020 Outpatient department appointment**
Smell Identification Test	5/16 (anosmia)	Not measured	Not measured	Not measured	Not measured	Not measured
CRS symptoms						
Nasal congestion	3	2	1	1	0	0
Smell impairment	3	0	3	0	0	0
Runny nose	2	0	0	0	0	0
Postnasal drip	2	0	0	0	0	0
SNOT-22 score	38	8	24	9	7	4
ACT Score	16	25	25	25	25	25

SC, Subcutaneous.
Score of CRS symptoms: 0: no symptoms; 1: mild symptoms; 2: moderate symptoms; 3: severe symptoms.

TABLE II. The dynamics of COVID-19 symptoms development by the patient receiving dupilumab and her husband

COVID-19-related events	Date	Dupilumab patient (53 y)	Patient's husband (50 y)
	March 11, 2020, to March 12, 2020	Visiting Barcelona	
	March 12, 2020, to Macrh 15, 2020	Visiting Lisbon	
COVID-19 symptoms	March 14, 2020	Onset of smell impairment	Onset of cough, shortness of breath
	March 14, 2020		onset of fever (axillary measurement, 38.0°C)
	March 16-19, 2020	Onset of fever (axillary measurement, 38.0°C)	
Use of antipyretics		Paracetamol 500 mg oral	Paracetamol 500 mg and ibuprofen 400 mg oral
	Match 14-18, 2020		Headache
	March 17-22, 2020	Cough	
COVID-19 viral PCR test (nasal swabs taken by the family physician)	March 16, 2020	COVID-19-PCR-test result positive	COVID-19-PCR-test result positive
COVID-19 viral PCR test (nasal swabs taken by the outpatient physician)	March 22, 2020	COVID-19-PCR-test result negative	COVID-19-PCR-test result negative

the start of therapy with dupilumab. Given the wash-out time of 22 hours, our patient was no longer under the direct anti-inflammatory influence of prednisolone. However, glucocorticoids can influence immunity, for instance, by inducing the apoptosis of proinflammatory monocytes.[8] It might be possible that this type of monocytes could contribute to a more severe course of COVID-19. However, present knowledge about the efficacy of glucocorticoids used to treat COVID-19 remains ambivalent.[9] According to the World Health Organization, patients with chronic lung diseases (such as asthma) seem to be more at risk for a severe course of COVID-19. Interestingly, a recent report from Wuhan indicated that none of the patients included in a sample of 140 patients affected by COVID-19 had asthma or allergic rhinitis[E1]; therefore, the severity level of COVID-19 could not be assessed in this particular group.

Particularly interesting is the course of the olfactory disorder. Before the treatment with dupilumab, the patient had respiratory anosmia caused by the obstruction of the olfactory region by nasal polyps. A significant recovery of olfactory function occurred already after the second dose of dupilumab. Anosmia was the first sign of COVID-19 in the absence of other typical symptoms. After the patient's recovery, she regained the function of the olfactory system. Interestingly, anosmia is described as occurring in up to two-thirds of patients with COVID-19 in the affected countries.[E2,E3] The patients report a sudden onset of almost complete loss of the olfactory function. However, so far, this has only been determined while collecting patients' medical history and not through validated smell tests. The pathomechanism of the olfactory dysfunction during COVID-19 is not yet known. Nevertheless, a newly occurring olfactory disorder should be assessed as an essential symptom of COVID-19, and the patients affected by anosmia should be regarded as infectious until tested for COVID-19.

In summary, we delivered the first piece of evidence supporting the view that patients with severe CRSwNP can continue to be treated with dupilumab during COVID-19. Emerging information about the course of SARS-CoV-2/COVID-19 in patients with CRSwNP should further facilitate the decision-making process about the continuation of therapy with dupilumab.

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Serum folate metabolites, asthma, and lung function in a nationwide US study

To the Editor:

Folate is a major dietary source of the methyl donors needed to form *S*-adenosylmethionine from homocysteine. Unlike folate from natural dietary sources, folic acid from fortified food or supplements requires dihydrofolate reductase (DHFR) to be reduced to tetrahydrofolate, which can then be metabolized to 5-methyl-tetrahydrofolate (5-MTHF), the main circulating folate form involved in DNA methylation (see Fig E1 in this article's Online Repository at www.jacionline.org). Unmetabolized folic acid (UMFA) in serum may occur as a result of consumption of excess folic acid (~300 μg), which saturates DHFR in the body.[1]

There is inconsistent evidence of adverse effects of folic acid supplementation on asthma or allergy in children, and little is known about folate and asthma in adults.[2] We examined the relation between serum levels of total folate and folate metabolites (5-MTHF and UMFA) and current asthma or lung function among children and adults who participated in the National Health and Nutrition Examination Survey (NHANES). We also investigated whether the ratio of serum 5-MTHF level to serum UMFA level is associated with asthma or lung function in this population.

NHANES is a cross-sectional nationwide survey of a representative sample of the US population. Ethnic minorities, low-income whites, and individuals aged 80 years and older are oversampled. NHANES was approved by the institutional review board of the US Centers for Disease Control and Prevention. Informed consent was obtained from all study participants. Data from subjects who participated in NHANES 2011-2016 and who did not report being pregnant were included in the current analysis.

Different folate forms in serum (total folate level, 5-MTHF level, UMFA level, and ratio of 5-MTHF to UMFA) were measured by isotope dilution high-performance liquid chromatography coupled to tandem mass spectrometry, as described in the NHANES laboratory procedure manual (https://wwwn.cdc.gov/nchs/data/nhanes/2007-2008/labmethods/FOLFMS_E_MET.PDF).

Current asthma was defined by a positive answer to both of the following questions: "Has a doctor or other health professional ever told you that you have asthma?" and "Do you still have asthma?" Spirometry was available for subjects aged 6 to 79 years who participated in NHANES 2011-2012. Eligible participants underwent spirometry following American Thoracic Society recommendations. Percent predicted FEV_1, forced vital capacity (FVC), and FEV_1/FVC ratio were calculated by using Global Lung Initiative 2012 equations that account for age, sex, race/ethnicity, and height.[3]

Sampling weights, stratification, and clusters provided by the NHANES were incorporated into the analysis. Wald chi-square tests and *t* tests were used for bivariate analyses. The Spearman rank correlation coefficient (*r*) was used to examine the correlation between folate metabolites. Multivariable logistic regression was used for the analysis of quartiles of serum levels of folate forms and current asthma. All multivariable models were adjusted for age, sex, race/ethnicity, annual household income, body mass index (BMI) (in adults) or BMI *z* score (in children), family history of asthma, season of sampling, serum cotinine level, and (in adults) pack-years of cigarette smoking. Because of significant linear trends in the bivariate analyses of quartiles of folate forms and lung function measures, folate forms were treated as ordinal (continuous) variables for the multivariable linear regression analysis of lung function. All statistical analyses were conducted by using the SAS SURVEY procedure and SAS software, version 9.4 (SAS Institute, Cary, NC).

The current analysis included 5,933 children (aged 6 to 19 years) and 12,739 adults (aged 20 to 79 years) (see Fig E2 in this article's Online Repository at www.jacionline.org). Of these participants, 1642 children and 3502 adults from NHANES 2011-2012 had spirometry data and were included in the analysis of lung function measures. A comparison of the characteristics of subjects who were and were not included in this analysis is shown in Table E1 (available in this article's Online Repository at www.jacionline.org).

Compared with children without current asthma, those with asthma were more likely to be non-Hispanic black and to have a family history of asthma, higher BMI *z* score, lower ratio of serum 5-MTHF level to serum UMFA level, and lower FEV_1 and FEV_1/FVC ratio (see Table E2 in this article's Online Repository at www.jacionline.org). Compared with adults without current asthma, those with asthma were more likely to be female and non-Hispanic white or black and to have a family history of asthma, an annual household income less than $20,000, higher

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TABLE E1. A white blood cell count and differential

Parameter	Before the infection September 30, 2019	After COVID-19 diagnosis April 7, 2020	COVID-19–free April 22, 2020
HgB (g/dL)	14.20	7.90	13.30
HCT (%)	41	36	38
Erythrocytes	4.70	4.06	4.30
WBC ($\times 10^9$/L)	10.40	6.80	7.20
Thrombocytes (absolute)	411.00	404.00	301.00
Neutrophils (absolute) ($\times 10^9$/L)	6.64	3.6	3.46
Lymphocytes (absolute) ($\times 10^9$/L)	2.8	2.52	2.73
Monocytes (absolute) ($\times 10^9$/L)	0.62	0.47	0.48
Eosinophils (absolute) ($\times 10^9$/L)	0.17	0.22	0.24
Basophils (absolute) ($\times 10^9$/L)	0.06	0.10	0.06
Neutrophils (%)	63.8	52.6	49.3
Lymphocytes (%)	26.9	37.1	38.8
Monocytes (%)	6.0	6.9	6.8
Eosinophils (%)	2.1	2.5	3.4
Basophils (%)	0.6	0.9	0.9

HCT, Hemotacrit; *WBC*, white blood cell.