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COVID-19 in a series of patients with aspirin-exacerbated respiratory disease

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Clinical Implications

- We report a series of patients with aspirin-exacerbated respiratory disease who became infected with severe acute respiratory syndrome coronavirus 2. Most of these patients had been treated with biologics for their baseline respiratory disease and did not appear to experience increased morbidity related to coronavirus 2019.

Early in the severe acute respiratory syndrome coronavirus (SARS-CoV-2) pandemic, asthma was understood to be a risk factor for poor outcomes in those infected. Yet, as understanding of the disease matured, asthma was not consistently observed as a risk factor. Because asthma is a heterogeneous disorder, asthma endotypes may impact coronavirus 2019 (COVID-19)-related morbidity.

Aspirin-exacerbated respiratory disease (AERD) is an inflammatory disorder characterized by nasal polyposis and asthma, defined by hypersensitivity to nonsteroidal anti-inflammatory drugs, and is associated with high levels of type 2 inflammation involving mast cell and eosinophil activation. AERD is enriched in populations with severe asthma and is also recognized as the most likely endotype to experience severe and early nasal polyp recurrence, making this group of patients much more difficult to control.¹ Given this burden of illness, we evaluated the morbidity associated with SARS-CoV-2 infection in our respective AERD cohorts.

A total of 19 patients with AERD were identified with SARS-CoV-2 infection documented by PCR, convalescent antibody testing, or compatible clinical syndrome after close exposure to a known case (Table 1). Respiratory biologic use was common (15 of 19) and was continued throughout infection with SARS-CoV-2. All but 1 patient met criteria for severe asthma based on FEV₁ impairment or need for biologic or systemic corticosteroid therapy. Of the 16 symptomatic infections, 2 patients required hospitalization, and all other patients experienced mild to moderate self-limited symptoms. Some reported residual health effects between 2 and 11 months from infection. Our cohort sample is not large enough to analyze statistically, but a few cases merit closer review.

A 53-year-old obese man was on baseline dupilumab therapy when he developed severe COVID-19 pneumonia and a moderate asthma exacerbation. He was hospitalized for severe hypoxia complicated by a pulmonary embolism. Before hospitalization he had impairment in FEV₁ (77%), a normal Sino-Nasal Outcome Test-22 score of 7, and an elevated

absolute eosinophil count of 980 cells/ μ L. While hospitalized, he was treated with remdesivir, dexamethasone, supplemental O₂, and enoxaparin sodium and then was transitioned to oral apixaban for the pulmonary embolism. At the time of publication, he has returned to his pre-COVID baseline medications and oral apixaban.

A 75-year-old woman with diabetes on anticoagulation was hospitalized. At baseline, she was treated with benralizumab and had received 2 systemic corticosteroid bursts in the year before infection. Baseline FEV₁, asthma control test score of 20, and Sino-Nasal Outcome Test-22 score suggested reasonable baseline airway control. She was treated with remdesivir and dexamethasone and at the time of publication is still requiring home oxygen.

A 54-year-old diabetic woman with hypertension, morbid obesity, corticosteroid-dependent asthma, impaired baseline lung function on dupilumab, and a long-term taper of hydrocortisone contracted SARS-CoV-2 and was treated with a prednisone taper and doxycycline for COVID-19 pneumonia. She recovered after 2 weeks and did not require supplemental oxygen or hospitalization.

A 55-year-old man with hypereosinophilia and coronary artery disease was on maintenance treatment with benralizumab. He had required 6 courses of systemic corticosteroids in the previous year due to poor airway control and asthma exacerbations. His COVID-19 infection was asymptomatic.

A 74-year-old man with Parkinson disease, coronary artery disease, and baseline impairment in lung function was on dupilumab at the time of his COVID-19 infection. He experienced cough and worsening shortness of breath as well as significant fatigue. Despite this, he did not require oxygen or hospitalization, nor did he develop any severe complication.

Type 2 inflammation may influence the course of COVID-19 in several ways. SARS-CoV-2 uses the angiotensin-converting enzyme 2 (ACE2) receptor for cell entry, a receptor present throughout the respiratory epithelium, with host transmembrane protease serine 2 (TMPRSS2) providing cleavage of the spike protein, which is required for virus fusion. These proteins are influenced by type 2 immune processes, with IL-13 decreasing ACE2 levels and increasing TMPRSS2 levels.² Consistent with the hypothesis that high type 2 inflammation could have a modifying effect, patients with asthma presenting to the emergency department with COVID-19 and a prior absolute eosinophil count of 150 cells/ μ L were less likely (odds ratio, 0.46) to be admitted to the hospital. Hospitalized patients with absolute eosinophil count of less than 150 cells/ μ L were also significantly less likely to die (odds ratio, 0.006).³ Most of our cohort members were on an asthma biologic (79%) yet experienced predominantly mild infection, suggesting that the underlying disease process might be protective independent of biologic-induced dampening of the type 2 signal. Yet, in another study, there did not appear to be a difference in ACE2 and TMPRSS2 expression in patients with asthma versus healthy controls, but male sex, Black/African American race, and diabetes mellitus were associated with higher ACE2 and TMPRSS2 gene expression.⁴

TABLE I. Clinical characteristics of SARS-CoV-2 infection in AERD

| Age/sex | Ethnicity | Comorbidities* | Biologics/systemic corticosteroids/inhaler type/LTMD | Aspirin dose [†] /duration | Sinus surgery/recent surgery [‡] | SNOT-22 score | FEV ₁ (% pred) | AEC (cells/ μ L) | COVID outcome | "Long-haul" symptoms |
|---------|--------------------|---|--|-------------------------------------|---|---------------|---------------------------|----------------------|---|----------------------|
| 17F | Non-Hispanic White | None | ICS | 1300mg 10 mo | 1 sx Not recent | 6 | 98 | 730 | Mild outpatient | N |
| 18F | Non-Hispanic White | None | Dupilumab, ICS/LABA | N | 1 sx | 47 | 91 | 170 | Mild outpatient | N |
| 36F | Non-Hispanic White | Hypothyroid | Dupilumab Methylprednisolone, ICS/ LABA, LTMD | N | 0 | 52 | 81 | NA | Moderate emergency room | N |
| 36M | Black/AA | HTN, obesity | Dupilumab, hydrocortisone, ICS/ LABA | N | 5 sx Not recent | NA | 54 | 1600 | Asymptomatic | N |
| 37F | Non-Hispanic White | None | Benralizumab, ICS/ LABA, LTMD | 650 mg 3 y | 2 sx Not recent | 13 | 97 | NA | Mild outpatient | N |
| 37F | Non-Hispanic White | Pre-DM, morbid obesity, OSA | Dupilumab, ICS/LABA | N | 2 sx Not recent | 60 | 111 | 340 | Moderate outpatient | Y, Fatigue |
| 39F | Non-Hispanic White | CSU, chronic otitis media, psoriasis | Dupilumab Omalizumab No other controllers | 325 mg 3 y | 7 sx Not recent | 31 | 91 | 560 | Mild outpatient | N |
| 42M | Asian | Hypothyroid | ICS/LTMD | 1300mg 9 y | 1 sx Not recent | 64 | 52 | 460 | Mild outpatient | N |
| 43M | Non-Hispanic White | Non | Dupilumab, ICS/LABA, LTMD | 1300mg 2 y | 2 sx Not recent | 8 | 92 | 650 | Mild outpatient | Y, Fatigue |
| 50F | Non-Hispanic White | HTN, pre-DM | ICS/LABA | N | 1 sx Recent | 52 | 93 | 280 | Mild outpatient | Y, Fatigue |
| 50F | Non-Hispanic White | None | Mepolizumab, ICS/ LABA, LTMD | 650 mg 2 y | 0 surgery | 10 | 97 | NA | Mild outpatient | N |
| 50F | Non-Hispanic White | HTN | ICS/LABA | 1300mg 10 y | 0 surgery | NA | 57 | 1350 | Moderate outpatient | N |
| 53F | Non-Hispanic White | None | Dupilumab, ICS/LABA | 325 mg 3 y | 4 sx Not recent | NA | 52 | 900 | Asymptomatic | N |
| 53M | Non-Hispanic White | Obesity | Dupilumab, ICS/LABA | N | 2 sx Not recent | 7 | 77 | 980 | Severe, hospitalized, COVID- related pneumonia, pulmonary embolus | Y, Fatigue |
| 54F | Black/AA | DM, obesity | Dupilumab, hydrocortisone, ICS/ LABA | N | 10 sx > Not recent | NA | 75 | 1500 | Moderate Outpatient | Y, Fatigue |
| 55M | Non-Hispanic White | HTN, CAD, hypereosinophilia, food allergy | Benralizumab ICS/LABA/LTMD | 1300mg 11 mo | 1 sx Not recent | 1 | 80 | 0 | Asymptomatic | N |

(continued)

TABLE 1. (Continued)

| Age/sex | Ethnicity | Comorbidities* | Biologics/systemic corticosteroids/inhaler | | Aspirin dose†/duration | Sinus surgery/recent surgery‡ | SNOT-22 score | FEV ₁ (% pred) | AEC (cells/μL) | COVID outcome | "Long-haul" symptoms |
|---------|--------------------|--------------------|--|--------------|------------------------|-------------------------------|---------------|---------------------------|----------------|---------------------|----------------------|
| | | | type/LTMD | type/LABA | | | | | | | |
| 57F | Black/AA | None | Dupilumab, ICS/LABA | N | N | 3 sx Not recent | NA | 74 | 200 | Moderate outpatient | N |
| 74M | Non-Hispanic White | Parkinson, CAD, HL | Dupilumab, ICS/LABA/LAMA | 325 mg >10 y | 1 sx Not recent | NA | NA | 58 | NA | Moderate outpatient | N |
| 75F | Non-Hispanic White | HTN, DM, HL, Afib | Benralizumab, ICS/LABA, LTMD | N | 2 sx Not recent | 9 | 102 | 0 | 0 | Severe hospitalized | Y, Oxygen dependent |

AA, African American; AEC, absolute eosinophil count; Afib, atrial fibrillation; CAD, coronary artery disease; CSU, chronic spontaneous urticaria; DM, diabetes mellitus; HL, hyperlipidemia; HTN, hypertension; ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; LTMD, leukotriene modifier drug; N, no; *pre-DM*, pre-diabetes mellitus; *pred*, predicted; OSA, obstructive sleep apnea; *SNOT-22*, Sino-Nasal Outcome Test 22; Y, yes.

Mild = significant COVID-19 symptoms < 7 d, no need for significant medical intervention.

Moderate = significant COVID-19 symptoms ≥ 7 d and/or need for emergency room care or multiple outpatient medical visits.

Severe = hospitalization/intensive care, and/or oxygen requirement.

*All patients had a confirmed diagnosis of AERD including sinonasal polyposis, persistent asthma, and nonsteroidal anti-inflammatory drug reactivity. Data reported represent the last reported value before COVID-19 diagnosis.

†Aspirin dose is typically divided in half and taken twice daily, except 325 mg, which is given once daily.

‡Recent surgery = sinus surgery within 6 mo of COVID-19 infection.

Asthma exacerbations are frequent after viral respiratory infections. Whether this would be true following SARS-CoV-2 infections was the topic of much discussion, yet current data suggest that asthma exacerbations from SARS-CoV-2 are not a common contributor to morbidity.⁵ Notably, our cohort with moderate to severe asthma required few systemic corticosteroids following COVID-19 illness.

Asthma is not overrepresented in cohorts of patients with severe SARS-CoV-2 infection.⁶ Yet, some data do generate concern regarding the outcomes in asthmatic and allergic patients. In a Korean cohort study of 219,959 subjects who underwent COVID-19 testing, asthma and allergic rhinitis were associated with increased risk of test positivity and worsened clinical outcomes.⁷ A similarly large database (>17 million patients) noted an increased risk of COVID-19–related death in patients with asthma, but only those with recent oral corticosteroid use.⁸ In a review of 634 Dutch patients with asthma on respiratory biologic therapy during the initial wave of the pandemic, 9 were diagnosed with COVID-19 of which 7 required hospitalization, 5 required intubation, and 1 patient died. These reports suggest that COVID-19 morbidity in patients with severe asthma on biologic therapy could be quite high.⁹ Regional and temporal differences in testing availability for asymptomatic or mild cases, treatment and health care resource availability, and prevalence of high-risk comorbidities make generalizability of these reports difficult.

Collectively, the authors follow a large cohort of approximately 1000 patients with AERD. In these combined cohorts, COVID-19 infection did not appear to have higher morbidity than what is seen in the general population. This is reassuring in a group of patients with exacerbation-prone asthma. It is intriguing that a strong type 2 signal might be protective—a signal that the vast majority of patients with AERD exhibit. Yet, our cohort is not large enough to draw firm conclusions. Whether specific treatments that skew type 2 immune patterns might be influential in SARS-CoV-2 infection remains to be seen.

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