Summary

- There are currently no available data regarding the risk of infection with the new Coronavirus disease (COVID-19) in patients being treated with benralizumab, and only limited data on the severity or progression of disease in patients treated with benralizumab who are exposed to, or infected with SARS-CoV-2 (Severe acute respiratory syndrome coronavirus 2).

- The American Academy of Allergy, Asthma and Immunology (AAAAI) provides the following recommendations in a recently published resource for clinicians pertaining to COVID-19 (https://education.aaaai.org/resources-for-a-i-clinicians/covid-19):1
  - There is no evidence which suggests immune response to COVID-19 will be impaired in asthma patients treated with anti-interleukin (anti-IL)-5Ra therapy.
  - In the absence of any data indicating a potential for harm, it would be reasonable to continue administration of biologic agents during the COVID-19 pandemic, in patients for whom such agents are clearly indicated and have been associated with efficacy.

- Published case reports describe 5 occurrences of patients contracting SARS-CoV-2 while receiving benralizumab treatment for severe eosinophilic asthma. The range of symptoms experienced by each patient varied, but all developed a fever. The treatments administered also differed. In the 3 cases where detailed information was provided, patients were noted to be asymptomatic within 2 weeks. All 5 patients recovered.2,3,4

- AstraZeneca cannot provide advice or recommendations for the management of individual patients. Providers should use their clinical judgement to weigh the risks vs benefits of interrupting or initiating benralizumab therapy in individual patients, considering the broader clinical context of the patient.
  - In Phase III clinical studies, a single dose of benralizumab administered every 8 weeks was allowed to be missed, with the next dose given according to regular schedule.5,6,7 In the absence of data for 2 or more missed doses from Phase III studies, health care providers should determine the scheduling of benralizumab dosing after a treatment interruption, that was not a result of a perceived treatment-related adverse event, based on their clinical judgement and in accordance to the labeled indication (i.e. severe asthma with an evidence of an eosinophilic phenotype) and posology.
  - Benralizumab 30 mg subcutaneously (SC) has been evaluated for use in a single-dose prefilled syringe and a single-use autoinjector (AI) device in phase 3 clinical trials.
  - A patient may self-inject or their caregiver may administer benralizumab, using the prefilled AI device after proper training in subcutaneous injection technique, and after the healthcare provider determines it is appropriate.

- Please also see https://www.who.int/health-topics/coronavirus for ongoing updates, information and guidance from the World Health Organization (WHO) related to the COVID-19 outbreak.

Background

Benralizumab is an anti-eosinophil, humanised afucosylated, monoclonal antibody (IgG1, kappa). It binds to the alpha subunit of the human interleukin-5 receptor (IL-5Ra) with high affinity and specificity. The IL-5 receptor is specifically expressed on the surface of eosinophils and basophils. The absence of fucose in the Fc domain of benralizumab results in high affinity for FcyRIII receptors on immune effector cells.
such as natural killer (NK) cells. This leads to apoptosis of eosinophils and basophils through enhanced antibody-dependent cell-mediated cytotoxicity (ADCC), which reduces eosinophilic inflammation. It is currently indicated for the treatment of severe eosinophilic asthma.\(^8\)

Coronaviruses (CoV) are a large family of viruses that cause illness ranging from the common cold to more severe diseases such as Middle East Respiratory Syndrome (MERS-CoV) and Severe Acute Respiratory Syndrome (SARS-CoV).\(^9\) SARS-CoV-2, the novel virus causing the disease COVID-19, is a new strain that was discovered in 2019 and has not been previously identified in humans.\(^10\) Infection can result in respiratory tract symptoms that can be severe.

**Clinical Data**

**Susceptibility to SARS-CoV-2 infection & impact on the clinical severity of COVID-19 respiratory disease**

There are currently no available data regarding the risk of infection with COVID-19 in patients being treated with benralizumab, and limited data on the severity or progression of disease in patients treated with benralizumab who are exposed to, or infected with SARS-CoV-2.

A role for eosinophils in the immune response to COVID-19 is unknown. Available case reports to date suggest that blood levels of eosinophils and lymphocytes can be decreased during the acute phase of COVID-19 infection and then return towards normal in patients whose symptoms improve.\(^11,12,13,14,15\) It has been hypothesized that the initial blood eosinophil lowering may be a result of stress response related to acute lung injury caused by COVID-19.\(^13\) Based on available reports, eosinophilia does not appear to be a general feature of COVID-19-related lung pathology: available reports are either silent on the presence of eosinophils in the tissue\(^12,16\) or have noted minimal lymphocytes, eosinophils and neutrophils.\(^17\) Taken together, although the current data are limited, there is little indication that eosinophils have a protective or exacerbating role in COVID-19 disease.

Regular administration with benralizumab does not result in clinically meaningful changes in non-IL-5 receptor bearing cells such as lymphocytes or neutrophils.\(^18\) There was no meaningful difference in overall infections or severe infections, including typical viral infections between benralizumab and placebo in the approximately 1 year, placebo-controlled, asthma exacerbation studies, with no new signals related to reported infection during a second year of treatment.\(^19,20,21,22\)

**Case Reports**

Renner A et al. *J Asthma. 2020.*\(^2\)

This report describes the case of a 41-year-old male patient diagnosed with severe eosinophilic asthma, who was on benralizumab for 2 years with good asthma control. Prior to treatment with biologics, the patient experienced multiple exacerbations per year triggered by viral infections, which all required OCS. Other than chronic rhinosinusitis with nasal polyps, the patient had no additional known comorbidities.

During the COVID-19 pandemic, the patient developed a high fever and tested positive for SARS-CoV-2. The first symptoms the patient experienced (Day 1) were exertional dyspnea and fatigue while jogging, which resolved by Day 2. On the morning of Day 3, the patient developed a fever of 39°C, resting dyspnea and back pain. All symptoms resolved by Day 6 and treatment with oral corticosteroids was not needed. On Day 12 a nasopharyngeal swab was taken and returned positive for SARS-CoV-2.
The patient’s asthma control questionnaire 6-item scale worsened moderately in the week of the infection and returned to normal levels thereafter. An asthma control test, measuring longer term asthma control, showed no decline.


The cases of two severe asthma patients on treatment with benralizumab, affected by COVID-19 are documented:

The first report describes the case of a 56-year-old female diagnosed with late-onset, severe, eosinophilic asthma with bronchiectasis (without criteria for asthma-COPD overlap syndrome), whose asthma was controlled with high dose inhaled corticosteroids, long-acting beta2-agonist, montelukast, ipratropium and benralizumab.

The patient presented at the emergency room after a 24-hour episode of fever, arthralgia, myalgia, dyspnea and brownish expectoration. Wheeze and hypoxemia were absent. Tests detected a unilobar opacity in the right lung, a slightly increased C-Reactive Protein (CRP) and lactate dehydrogenase (LDH). The patient tested positive for SARS-CoV-2 and was started on levofloxacin 500 mg for 14 days, and systemic corticosteroids (1mg/kg) were administered due to the brownish expectoration and history of bronchiectasis. The patient was discharged on the 4th day of treatment with oral corticosteroids, and was asymptomatic a week later.

The second report describes the case of a 62-year-old male with severe eosinophilic asthma on treatment with benralizumab. Comorbidities included moderate obstructive sleep apnea, chronic rhinosinusitis with nasal polyps, bronchiectasis and obesity. On development of a cough, fever, darker and thicker than usual expectoration, he self-medicated with levofloxacin 500 mg for 3 days. Due to lack of improvement of symptoms, the patient was evaluated at primary care; a chest x-ray showed peripheral and bilateral opacities indicative of COVID-19 related pneumonia.

The patient was referred to the emergency room where tests showed lymphopenia with increased levels of LDH, CRP, D40 dimers, fibrinogen and a baseline pO2 of 59 mmHg. A diagnosis of SARS-CoV-2 infection was presumed based on the clinical and temporal context. The patient requested voluntary discharge and isolated at home with monitoring by his primary care physician. He was treated with azithromycin 500 mg (3 days), hydroxychloroquine 200 mg twice a day (5 days) and amoxicillin-clavulanic 875/125 mg (7 days). The patient was asymptomatic a week later.

Heffler E et al. *Asthorea.* 2020.4

A study investigating the incidence of COVID-19 cases in a large population of patients with severe asthma in Italy, identified 2 patients (1 confirmed; 1 highly suspected) with COVID-19. A summary of the cases is provided in the following table.
TABLE: Summary of 2 patients with severe asthma and COVID-19 infection.

<table>
<thead>
<tr>
<th>COVID-19 Status</th>
<th>Age</th>
<th>Sex</th>
<th>Atopy</th>
<th>Comorbidities</th>
<th>Asthma Therapy</th>
<th>COVID-19 Symptoms</th>
<th>COVID-19 Therapy</th>
<th>COVID-19 Clinical Course</th>
</tr>
</thead>
</table>

ICS/LABA = inhaled corticosteroid/long-acting β2 adrenoceptor agonist; LAMA = long acting muscarinic antagonist; LTRA = leukotriene receptor antagonist.

**Relevant Labeling Information**

Please refer to the [FASENRA Prescribing Information](https://www.fasena.com/Pages/Patient-Resources/Patient-Education/COVID-19.aspx) for further product information including Warnings and Precautions.

**Reporting of Postmarketing Adverse Events**

It is AstraZeneca policy to provide AE information to health care professionals from the labeling information, the published literature, and clinical trial data for our marketed products. Key findings from the clinical trials, including safety information, form the basis for the labeling information. We generally do not provide specific AE information from the AstraZeneca Safety database because of the inherent limitations of spontaneous reports.

Such limitations include, but are not limited to AE recognition, underreporting, reporting biases, estimates of patient exposure, report quality, and lack of established causality of reported AEs. The safety profile of each AstraZeneca product is continuously monitored, and the labeling information is updated whenever new safety issues are identified.

**Adverse Events Reporting**

In order to monitor the safety of FASENRA, we encourage clinicians to report suspected adverse events to AstraZeneca at 1-800-236-9933.

Reference(s):

5 In House Data, AstraZeneca Pharmaceuticals LP. SIROCCO Clinical Study Protocol D3250C00017. October 2015.
6 In House Data, AstraZeneca Pharmaceuticals LP. CALIMA Clinical Study Protocol D3250C00018. March 2015.
8 FASENRA Prescribing Information.
18 Benralizumab Integrated Summary of Safety. 
19 In House Data, AstraZeneca Pharmaceuticals LP. Integrated summary of safety (Benralizumab [MEDI-563]). October 18, 2016.