FASENRA/FASENRA PEN-COVID-19

Summary

- There are currently limited data regarding the risk of infection with the Coronavirus disease (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 (Severe acute respiratory syndrome coronavirus 2).

- A few studies have reported that use of biologics (including benralizumab) for severe eosinophilic asthma were not associated with a higher risk of SARS-CoV-2 infection, nor with greater disease severity.\textsuperscript{1,2,3} However, one study has reported poor outcomes of SARS-CoV-2 infection in patients with severe asthma on biologics\textsuperscript{4} and another study reported that eosinophilia was protective from COVID-19 associated hospital admissions.\textsuperscript{5}

- A number of case reports of patients who contracted SARS-CoV-2 infection while receiving treatment with benralizumab have been published and are summarized for your review.\textsuperscript{6,7,8,10}

- The Global Initiative for Asthma (GINA) 2021 Report provides the following recommendation: It is important for patients to continue taking their prescribed asthma medications as usual during the COVID-19 pandemic. This includes ICS-containing medications (alone or in combination with a long-acting beta\textsubscript{2}-agonist [LABA]), and add-on therapy including biologic therapy for severe asthma.\textsuperscript{11}

- 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.

- 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-5R\textalpha) 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 Fc\gammaRIII 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.\textsuperscript{12}

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).\textsuperscript{13} 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.\textsuperscript{14} Infection can result in respiratory tract symptoms that can be severe.
**Clinical Data**

This information is intended to be a concise summation of representative clinical trial data, rather than being all-inclusive; therefore, all available published literature may not be incorporated into this response.

**Susceptibility to SARS-CoV-2 Infection & Impact on the Clinical Severity of COVID-19 Respiratory Disease**

There are currently limited data regarding the risk of infection with SARS-CoV-2 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 SARS-CoV-2 infection and then return towards normal in patients whose symptoms improve.\(^{15,16,17,18,19}\) 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.\(^{17}\) 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\(^{16,20}\) or have noted minimal lymphocytes, eosinophils and neutrophils.\(^ {21}\) 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.\(^ {22}\) 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.\(^ {23,24,25,26}\) An observational study of a cohort of 676 severe asthma patients from the Belgian Severe Asthma Registry reported that the use of biologics (benralizumab, n=98) for severe eosinophilic asthma was not associated with a higher risk of SARS-CoV-2 infection nor with greater disease severity. Fourteen patients (2.1%) were identified with SARS-CoV-2 infection confirmed by either positive polymerase chain reaction (PCR) and/or specific IgG, of which 5 had been hospitalized, of which 3 received supplemental oxygen therapy.\(^ {1}\)

A multicenter cohort study of 545 adults from Spain with severe asthma reported that patients receiving treatment with a biologic (benralizumab, n=98) did not have an increased risk of SARS-CoV-2 infection, or greater disease severity or mortality.\(^ {2}\) Thirty five patients (6.4%) were identified with SARS-CoV-2 infection confirmed by either PCR, or using antibodies test and compatible clinical symptoms, which was similar to the incidence in the general population/region (5.2%). Eight patients (22.9%) required hospital admission, of which 7 presented with pneumonia, of which 2 were severe. One patient required admission to the intensive care unit, and the other patient (82-year-old with hypertension, diabetes, and ischemic cardiopathy) died as a result of COVID-19 complications.

A review of data from a the Italian Severe Asthma Registry did not observe an increase in hospital admissions in 558 patients with severe asthma, of which 68.2% were receiving a biologic (benralizumab, n=78), compared to the general population. In addition, there was no significant increase in the incidence of SARS-CoV-2 infection in patients treated with high-dose ICS-LABA and biologics (7/129, 5.43%) compared to patients treated with ICS-LABA alone (0/60, 0%).\(^ {3}\)

A survey of the Dutch Severe Asthma Registry RAPSODI, evaluated 634 severe asthma patients who received biologic therapy (benralizumab, n=120), identified 9 patients diagnosed with SARS-CoV-2
infection, of which 7 (1.1%) required hospitalization for oxygen therapy and 5 were admitted to the intensive care for intubation and mechanical ventilation. The odds ratio of COVID-19 related hospitalization and intubation were reported to be 14 and 41 times higher, respectively, compared to the general population.\(^4\)

A retrospective analysis of hospital patients with a positive PCR test for SARS-CoV-2 reported that pre-existing eosinophilia (absolute eosinophil count \(\geq 150\ \text{cells/\mu L}\)) in asthmatic patients was protective from COVID-19 associated admission, and development of eosinophilia during hospitalization was associated with decreased mortality. This cohort had too few patients on monoclonal biologic agents for severe asthma to allow for analysis by treatment.\(^5\)

**Case Reports**

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<th>TABLE: Summary of Benralizumab Patients who contracted COVID-19 Infection.</th>
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<tr>
<td>Citations</td>
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<tr>
<td>Renner A et al. <em>J Asthma</em>. 2021. &amp; Renner A et al. <em>ERJ Open Res</em>. 2020.(^6,7)</td>
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ACQ-6 = asthma control questionnaire 6; ACT = asthma control test; bEOS = blood eosinophils; CRP = c-reactive protein; CRSwNP = chronic rhinosinusitis with nasal polyps; ER = emergency room; GP = general practitioner; ICS = inhaled corticosteroid; ICU = intensive care unit; LABA = long-acting β2 adrenoceptor agonist; LAMA = long-acting muscarinic antagonist; LDH = lactate dehydrogenase; LTRA = leukotriene receptor antagonist; OCS = oral corticosteroids; SCS = systemic corticosteroids; SEA = severe eosinophilic asthma.

**Relevant Labeling Information**

Please refer to the FASENRA Prescribing Information 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):

12. FASENRA Prescribing Information.


23 In House Data, AstraZeneca Pharmaceuticals LP. Integrated summary of safety (Benralizumab [MEDI-563]). October 18, 2016.

