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2020-10-01

Renner , A , Marth , K , Patocka , K , Idzko , M & Pohl , W 2020 , ' COVID-19 in two severe asthmatics receiving benralizumab : busting the eosinophilia myth ' , ERJ Open Research , vol. 6 , no. 4 , 00457-2020 . <https://doi.org/10.1183/23120541.00457-2020>

<http://hdl.handle.net/10138/326488>

<https://doi.org/10.1183/23120541.00457-2020>

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COVID-19 in two severe asthmatics receiving benralizumab: busting the eosinophilia myth

To the Editor:

Amidst the current pandemic there is only little clinical evidence regarding COVID-19 infections in asthma patients. Chinese data suggests that asthma patients might not be at an elevated risk of severe infections [1, 2]. A recent article by CARLI *et al.* [3] hypothesises that asthma might even have a protective effect in COVID-19 infections. It is important to point out that this is purely theoretical. Eosinophils from healthy probands have antiviral activity against respiratory syncytial virus and influenza virus, but not eosinophils collected from asthma patients [4]. Eosinopenia, alongside lymphopenia has been seen in COVID-19 patients [2]. Both eosinopenia and lymphopenia are more common in patients with COVID-19 pneumonitis compared with patients with non-COVID-19 viral pneumonitis [5]. AZKUR *et al.* [6] attribute this to an overwhelming type 1 response.

PETERS *et al.* [7] showed that angiotensin converting enzyme 2 (ACE2) and transmembrane protease serine 2 (TMPRSS2), two molecules previously identified to facilitate severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection of host cells [8], have a higher expression in the sputum of certain asthma patients (African Americans, males and diabetics) and a lower expression in the sputum of asthma patients receiving inhaled corticosteroids, even when controlled for disease severity [7]. This provides rationale for both potentially identifying at-risk populations and a protective effect of inhaled corticosteroids in asthma patients for COVID-19 infections that goes beyond improved asthma control. KIMURA *et al.* [9] showed that interleukin (IL)-13, a mediator of T2 high asthma and a target of the monoclonal antibody (mAb) dupilumab, decreases ACE2 and increases TMPRSS2, possibly resulting in a zero-sum effect.

The current evidence on asthma, eosinophilia, T2 inflammation, and COVID-19 from preclinical and epidemiological data paints contradicting pictures. The work of SABOGAL PIÑEROS *et al.* [4] suggests that eosinophils in asthmatics and non-asthmatics are not comparable in the context of viral infections. While the evidence for COVID-19 infections in severe asthma patients receiving mABs is only anecdotal, we believe that some important observations can be made.

In their recent publication, FÖRSTER-RUHRMANN *et al.* [10] presented the case of a mild COVID-19 infection in a patient receiving dupilumab for severe chronic rhinosinusitis with nasal polyps (CRSwNP). Based on the information provided in the case report it can be assumed that the patient suffers from aspirin-exacerbated respiratory disease, a distinct subtype of eosinophilic asthma. The authors hypothesised that an increase in blood eosinophils, a well-known effect of dupilumab treatment, might have had a protective effect during the COVID-19 infection. This misconception, based on a paper by LIU *et al.* [11], has led some to argue for the discontinuation of anti-IL-5/5R mABs in severe eosinophilic asthma patients. This has been strongly discouraged in a recent position paper by SHAKER *et al.* [12].

Two severe eosinophilic asthma patients receiving benralizumab at our severe asthma clinic have had COVID-19 infections. Both patients experienced a very mild disease course with minimal to no deterioration in asthma control. The case report of a 41-year-old male patient has recently been published



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Experience with very mild #COVID19 disease courses in two severe eosinophilic asthmatics with complete eosinophil depletion due to benralizumab treatment counters the recent theories that eosinophilia is protective in COVID-19 infections <https://bit.ly/3cnEFvg>

Cite this article as: Renner A, Marth K, Patocka K, *et al.* COVID-19 in two severe asthmatics receiving benralizumab: busting the eosinophilia myth. *ERJ Open Res* 2020; 6: 00457-2020 [<https://doi.org/10.1183/23120541.00457-2020>].

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by RENNER *et al.* [13]. A 66-year-old male patient with severe eosinophilic asthma and CRSwNP has received benralizumab since December 2018. Baseline blood eosinophilia before initiation of benralizumab was $380 \text{ cells}\cdot\mu\text{L}^{-1}$. Similar to our recently published case report, blood eosinophils were depleted immediately ($20 \text{ cells}\cdot\mu\text{L}^{-1}$ 24 h after treatment initiation, no detectable eosinophils thereafter) and asthma control improved rapidly (asthma control test 11 before treatment and >20 after treatment).

On 28 March 2020 the patient developed fever, anosmia and fatigue. Two SARS-CoV-2 PCR tests were taken on two different days, both were positive. The fever improved after a few days, anosmia and fatigue lasted 2 weeks. The patient did not experience any pulmonary symptoms, asthma control test and asthma control questionnaire 6-item scale were unchanged from before the infection (25 and 0, respectively). No increase in asthma medication was necessary.

In our opinion, two assumptions can be made from viewing these three cases together.

The first concerns the potential protective effect of mAb treatment in these patients. While there is little evidence that people with asthma are at an elevated risk of more severe COVID-19 infections, both the patient presented here, as well as the patient in RENNER *et al.* [13] regularly suffered from viral exacerbations before the initiation of benralizumab. Case reports, and even case series, only provide anecdotal evidence, but with a growing number of similar cases the strength of this evidence increases. We believe that this potential protective effect might be based on good asthma control rather than immunological mechanisms, which are different in benralizumab and dupilumab.

Secondly, both our patients had no detectable blood eosinophils due to benralizumab treatment at the time of COVID-19 infection. As pointed out in a recent review by LINDSLEY *et al.* [14] a protective effect of eosinophilia in COVID-19 infections seems unlikely. Thus, we believe that there is no protective effect of elevated blood eosinophils, at least in eosinophilic asthma patients, and that this did not contribute to the mild disease in the patient presented by FÖRSTER-RUHRMANN *et al.* [10].

More case studies, and if possible prospective data collections and formal analyses of severe eosinophilic asthma patients receiving mAb treatment with COVID-19 infections, are necessary to confirm the assumptions laid out above.

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Received: 1 July 2020 | Accepted after revision: 15 Sept 2020

Conflict of interest: None declared.

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