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Benralizumab for severe DRESS in two COVID-19 patients

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Clinical Implications

- This report provides first evidence for the IL-5Rα-blocking antibody benralizumab as a treatment option for severe drug rash with eosinophilia and systemic symptoms not responding to first-line treatment; proteomic serum analyses point toward substantial eosinophil- and T cell–related changes induced by the treatment.

Drug rash with eosinophilia and systemic symptoms (DRESS) is a rare severe hypersensitivity reaction that clinically manifests with exanthema, facial edema, enlarged lymph nodes, fever, and organ damage at variable degrees.[1] Eosinophil expansion in blood is a hallmark of DRESS, and eosinophil tissue infiltration a main contributor to the observed organ damage and dysfunction.[2] Although high-dose systemic glucocorticoids have not been evaluated in randomized clinical trials, they are currently the first-line therapy for DRESS with organ involvement. However, glucocorticoid-associated adverse events remain high and response rates are variable. Also, regardless of therapy, patients with DRESS have a high, 5% to 10%, mortality rate.[2] Here, we report the first use of benralizumab (Fasenra), an IL-5-receptor α-chain-specific humanized monoclonal antibody (IgG1k) initially approved for eosinophilic asthma,[3] in 2 patients with glucocorticoid-unresponsive DRESS occurring during coronavirus disease 2019 (COVID-19). The study was approved by the regional ethics review board (EK2020-01029) and conducted according to the Declaration of Helsinki.

Both patients were treated in the intensive care unit for acute respiratory distress syndrome due to COVID-19. Patient 1, a 54-year-old woman, developed prominent eosinophilia followed 3 days later by cutaneous and systemic DRESS syndrome features (Table I). Esomeprazole and piperacillin-tazobactam (details: Figure E1, *A*, available in this article's Online Repository at www.jaci-inpractice.org), initiated almost 6 weeks before DRESS onset and administered intermittently, were suspected as most potential culprit drugs and stopped immediately. Patient 2, a 58-year-old man with COVID-19-related multiorgan failure, developed widespread maculopapular skin lesions, facial swelling, severe eosinophilia, and hepatic dysfunction. The suspected potential culprit drug in his case was midazolam, which had been administered approximately 3 weeks before the symptoms started (Figure E1, *A*, available in this article's Online Repository at www.jaci-inpractice.org). In both patients, skin histopathology from cutaneous lesions on the trunk (Figure E1, *B*, available in this article's Online Repository at www.jaci-inpractice.org) demonstrated a mostly perivascular lymphohistiocytic infiltrate and eosinophils, compatible with a diagnosis of drug hypersensitivity reaction.[1] DRESS diagnosis was based on the RegiSCAR criteria (scores 7 and 8, respectively; Table I). In addition to discontinuing the potential culprit drugs, both patients received high-dose intravenous methylprednisolone (patient 1: 125 mg for 3 days, 70 mg for 4 days; patient 2: 125 mg for 3 days), without improvement. In the setting of worsening eosinophilia (Figure 1, *A*), deteriorating organ function, and exacerbation of their cutaneous eruption, the decision was made to initiate therapy with benralizumab (Fasenra; 30 mg subcutaneously). This decision was based on the rationale that IL-5/eosinophil axis inhibition has been reported as a successful treatment in platelet-derived growth factor receptor alpha-negative hypereosinophilia[4] and that IL-5, eosinophils, and the eosinophil degranulation marker eosinophilic cationic protein (ECP) were highly increased. Within 2 days after benralizumab administration, both patients showed a rapid and substantial drop in blood eosinophils and, as measured in patient 1, ECP (Figure 1, *A*, and Figure E2, available in this article's Online Repository at www.jaci-inpractice.org). This was paralleled clinically by an improvement of the patients' cutaneous eruption and a lowering of liver enzyme levels. Patient 1 continued to improve over the following 18 days. Patient 2, however, developed disseminated intravascular coagulation secondary to COVID-19 and died from cardiac arrest after massive bleeding 17 days after the administration of Fasenra.

To explore treatment-induced immunological changes, targeted serum proteomic studies were performed immediately before and 1 day after Fasenra administration (see this article's Online Repository at www.jaci-inpractice.org; Figure 1, *B*). This analysis revealed a significant reduction in levels of IL-5, IL-4, and several proteins related to cytotoxic T-cell responses and activation (CD8, tumor necrosis factor, tumor necrosis factor–related apoptosis inducing ligand, signaling lymphocytic activation molecule 1, and programmed cell death 1-ligand 1), as well as the neutrophil- and macrophage-attracting chemokines C-C chemokine ligand 3 and CXC chemokine ligand 6.

Our report suggests that IL-5Rα blockade (benralizumab) is a valuable therapeutic option in critically ill patients with massive expansion of eosinophils, if eosinophils are suspected to play a pathogenic role and symptoms exacerbate despite high-dose glucocorticoids (as a first-line treatment). Additional cases and studies are needed to determine the safety and efficacy of Fasenra and other monoclonal antibodies targeting the IL-5 axis[5,6] in this setting.

The context, in which our DRESS cases occurred, was peculiar, that is, developing in severely affected patients with COVID-19 with acute respiratory distress syndrome. It is conceivable that the severe acute respiratory syndrome coronavirus 2 contributed directly or indirectly, via induction of a cytokine storm, to the combination of eosinophilia, critical illness, and eosinophil-induced organ damage.[7] Eosinopenia has

TABLE I. Patient details

	Patient 1	Patient 2
General information		
Sex	Female	Male
Age (y)	54	58
Ethnicity	Caucasian (Central Europe)	Asian (China)
Pre-existing conditions	Diabetes mellitus type 2	Diabetes mellitus type 2 Multinodular goiter Moderate allergic asthma
COVID-19-related information		
COVID-19 diagnosis before DRESS onset (d)	42	29
Intubation (due to ARDS) before DRESS onset (d)	32	23
SARS-CoV2 RT-PCR at the time of DRESS diagnosis	Negative	Negative
Medications for COVID-19	Lopinavir/ritonavir Hydroxychloroquine	Hydroxychloroquine
Complications from COVID-19	ARDS Pulmonary embolism Heparin-induced thrombocytopenia Multiple venous thrombosis Megacolon with focal ischemia Hepatopathy	ARDS Hemorrhagic shock from upper gastrointestinal bleeding Acute renal insufficiency (AKI 3) Catheter-associated thrombosis Hepatopathy
DRESS characteristics		
RegiSCAR DRESS Score	7	8
Detailed DRESS features (at the time of diagnosis)		
Skin eruption (>50% body surface area)	Maculopapular exanthema	Maculopapular exanthema
Fever	Yes	Yes
Lymphadenopathy	No	Yes
Eosinophilia	$>1.5 \times 10^9$/L	$>1.5 \times 10^9$/L
Atypical lymphocytes	None	None
Organ involvement; lab values at the time of diagnosis		
Kidney	No; serum creatinin 40 μmol/L: eGFR 114 mL/min	Yes; serum creatinin 142 μmol/L: eGFR 47 mL/min
Liver	Yes; AST 196 U/L; ALT 263 U/L	Yes; AST 106 U/L; ALT 125 U/L
Lung	Yes; ARDS	Yes; ARDS
Heart/muscle	Yes; myoglobin 129 μg/L	Yes; myoglobin 813 μg/L
Pancreas	No; pancreatic amylase 7 U/L	No; pancreatic amylase 6 U/L, lipase 7 U/L
Other	None	None
Viral serologies at DRESS diagnosis (HHV6, EBV, CMV, HSV1/2, VZV)	Negative	Negative
Skin histopathology suggestive for DRESS	Yes	Yes
Previous history of drug allergies	None	None
First-line DRESS treatment	Intravenous methylprednisolone (125 mg 4 d, 70 mg 3 d)	Intravenous methylprednisolone (125 mg 3 d)
Outcome	Alive; still hospitalized (day 28 after DRESS diagnosis)	Death from cardiac arrest after hemorrhagic shock (day 17 after DRESS diagnosis)

Normal ranges of laboratory test values: serum creatinine: 62-106 μmol/L; creatinin kinase: <190 U/L; myoglobin: 28-72 μg/L; AST and ALT: <50 U/L; pancreatic amylase: 13-52 U/L; lipase: 13-60 U/L.

ALT, Alanine transaminase; *ARDS*, Acute respiratory distress syndrome; *AST*, aspartate aminotransferase; *COVID-19*, coronavirus disease 2019; *DRESS*, drug rash with eosinophilia and systemic symptoms; *eGFR*, estimated glomerular filtration rate; *RT-PCR*, real-time PCR; *SARS-CoV2*, severe acute respiratory syndrome coronavirus 2.

been shown in patients with COVID-19 with a severe disease course on the other hand, but it remains to be elucidated whether this association is pathophysiologically relevant or rather incidental.[8]

IL-5 is mainly produced by T helper 2 cells and is a critical mediator responsible for differentiation, activation, and, in synergy with other mediators, chemotaxis of eosinophils,[9] which considerably contribute to organ damage in DRESS. Our

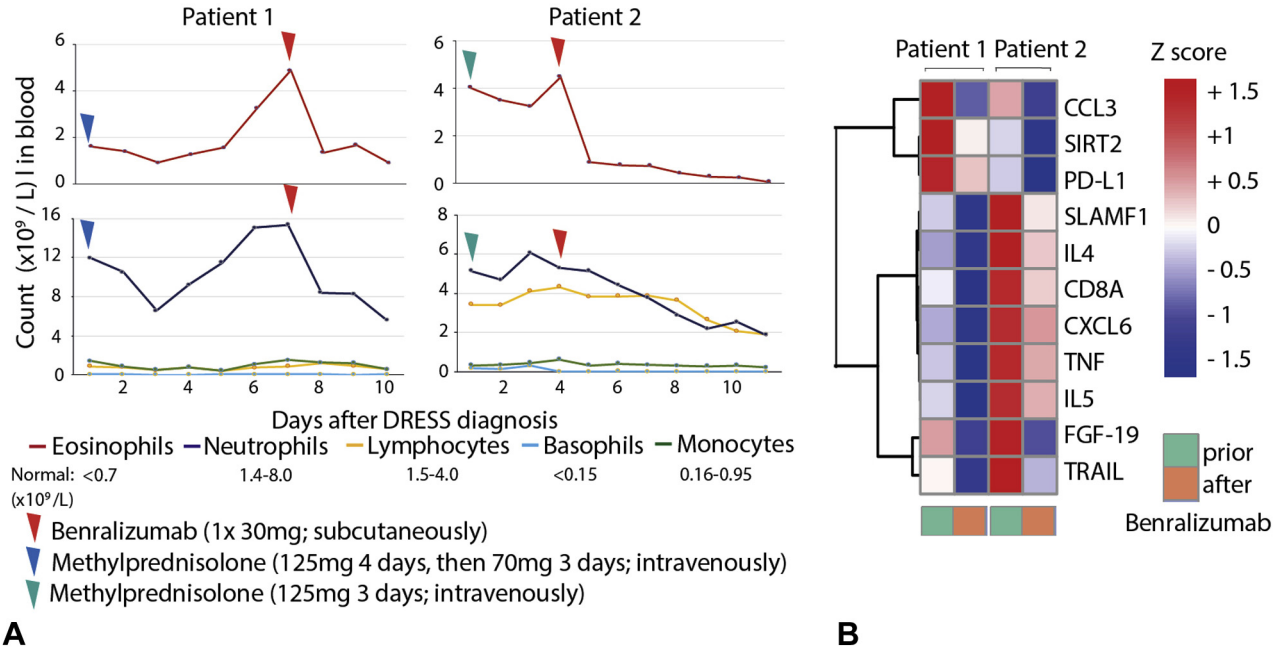

FIGURE 1. Serological changes during benralizumab therapy. **A**, Line graphs showing counts ($\times 10^9$/L) of the indicated leukocytes (measured daily) over the course of DRESS diagnosis and treatment in patients 1 and 2, respectively. **B**, Heatmap showing significantly up- and downregulated proteins (identified by Olink proteomics; $P < .05$) in patients 1 and 2 before (day 0) and after (day 1) treatment with benralizumab. *DRESS*, Drug rash with eosinophilia and systemic symptoms.

hematologic and proteomics data suggest that Fasenra had a rapid and profound effect on eosinophils. It also points toward a benralizumab-mediated indirect regulatory effect on other cell types, possibly cytotoxic T cells. It remains to be elucidated whether a similar dynamic is observed in other conditions during IL-5Rα blockade.

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The study was funded by the University Zurich.
Conflicts of interest: P. Schmid-Grendelmeier has received honorarium as participant at advisory boards from AstraZeneca. The rest of the authors declare that they have no relevant conflicts of interest.
Received for publication June 10, 2020; revised September 18, 2020; accepted for publication September 18, 2020.
Available online October 8, 2020.
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2213-2198

https://doi.org/10.1016/j.jaip.2020.09.039

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MATERIAL AND METHODS

Ethics approval

The study was approved by the regional ethics review board (EK2020-01029) and conducted according to the Declaration of Helsinki.

Sample preparation

Blood was collected using serum tubes. Samples were processed immediately after collection and stored at −80°C until further processing.

Protein quantification in blood

The proteomic Proseek multiplex assay by Olink (Uppsala, Sweden) is a proximity extension assay with oligonucleotide-labeled antibody probe pairs. It measures proteins via an antibody-mediated detection system linked to synthetic DNA for quantification by a real-time polymerase chain reaction platform.

Statistical analysis of Olink data

Olink data in normalized protein expression format were imported, processed by OlinkRPackage from Olink Proteomics (https://github.com/Olink-Proteomics/OlinkRPackage). The statistical comparison of protein levels between groups was performed with the Bioconductor limma package (https://bioconductor.org/packages/release/bioc/html/limma.html). The fold change and *P* value were estimated by fitting a linear model for each protein.

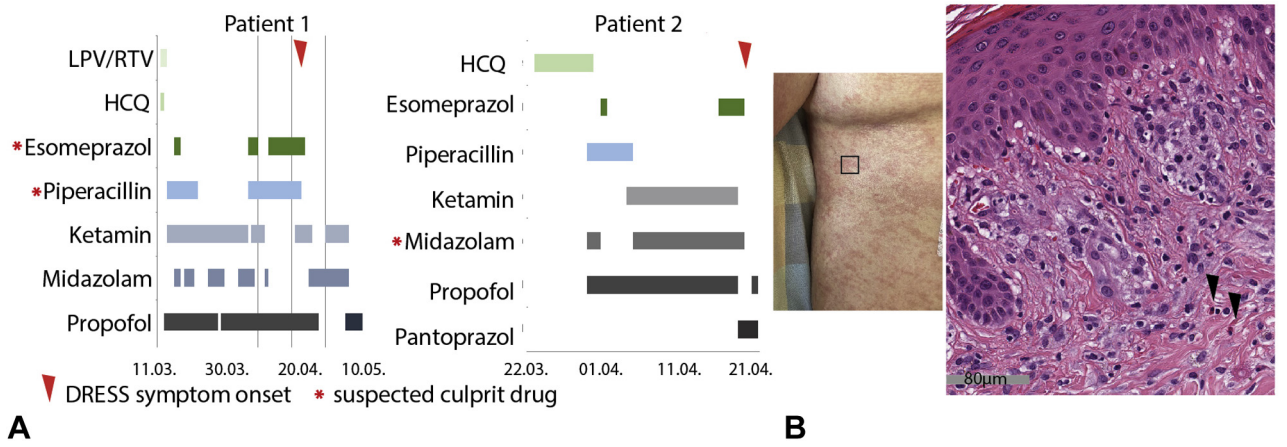

FIGURE E1. **A**, Timelines for the respective medications of patients 1 and 2. **B**, Hematoxylin/eosin staining from lesional skin of patient 2 (on the trunk, framed area on the photograph). Histopathology showing vacuolar changes of the basal layer and a mostly perivascular, lymphohistiocytic infiltrate with few admixed eosinophils (indicated by arrows) in the upper dermis. *DRESS*, drug rash with eosinophilia and systemic symptoms; *HCQ*, hydroxychloroquine; *LTV*, lopinavir; *RTV*, ritonavir.

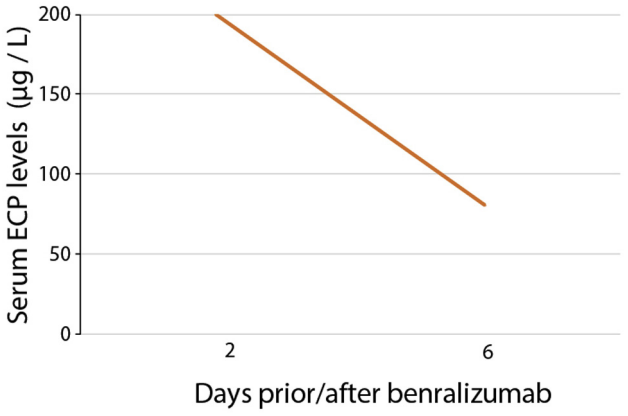

FIGURE E2. Levels of eosinophilic cationic protein (ECP) before (day 0) and at day 2 after benralizumab treatment in patient 1. The normal upper normal limit of ECP is 13.3 µg/L. On day 0, ECP levels exceeded the maximal measuring range (200 µg/L).