polyangiitis-like symptoms in this case series. The rapid recovery of eosinophil levels in a pro-IL-5/eotaxin milieu and the presence of other redundant cytokines might have contributed to sudden eosinophil recruitment and activation after anti-IL-5/IL-5R discontinuation. Switching from an anti-IL-5/IL-5R biologic to anti-IL-4-R-alfa should be carefully assessed in every patient in a personalized approach tailored to obtain severe asthma control and OCS tapering, to avoid severe eosinophilic complications.

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Reply to "The immunology of switching biologics in severe eosinophilic asthma patients"

To the Editor:

We appreciate the response from Spadaro et al[1] concerning our recent publication, 'Complications of switching from anti-IL-5 or anti-IL-5R to dupilumab in corticosteroid-dependent severe asthma."[2] The authors list a number of possible immunologic mechanisms that might have contributed to the eosinophilic complications we observed in the patients in our study. Currently, we can only speculate about the underlying pathophysiology of these complications. The proposed mechanisms of the authors are plausible. However, we believe that the lack of sufficient immunosuppressive treatment (oral glucocorticoids or other) in an active underlying eosinophilic disease (eg, eosinophilic granulomatosis with polyangiitis) may be sufficiently explanatory for the events in the patients in our study. This hypothesis is supported by the observation that in all patients in our study, symptoms could be readily suppressed after resuming treatment with (the same dose) of anti-IL-5. Nonetheless, the letter by Spadaro et al is great valuable for generating hypotheses. It is clear that we still have much to learn about the immunology of switching between biologics for severe asthma. More insight into the pathogenesis as well as additional real-world data may assist in identifying patients at risk for severe eosinophilic complications. Until then, close monitoring of patients who are switched from anti-IL-5(R) biologics to dupilumab remains essential.

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Benralizumab: A potential tailored treatment for life-threatening DRESS in the COVID-19 era

To the Editor:

We read with great interest the article by Schmid-Grendelmeier et al[1] who reported on IL-5Rα blockade with benralizumab in 2 patients with coronavirus disease 2019 (COVID-19) with refractory drug rash with eosinophilia and systemic symptoms (DRESS), and would like to share our experience of a similar case successfully treated with benralizumab.

A 43-year-old man with no past medical history presented with high-grade fever, multiple enlarged nodes, diffuse maculopapular exanthema with histologic evidence of eczematiform toxidermia, facial edema, parotitis, acute kidney failure, eosinophilic pneumonia (560,000 cells/mm^3, eosinophils: 15% on bronchoalveolar lavage), vasoplegic shock (with capillary leak syndrome), and

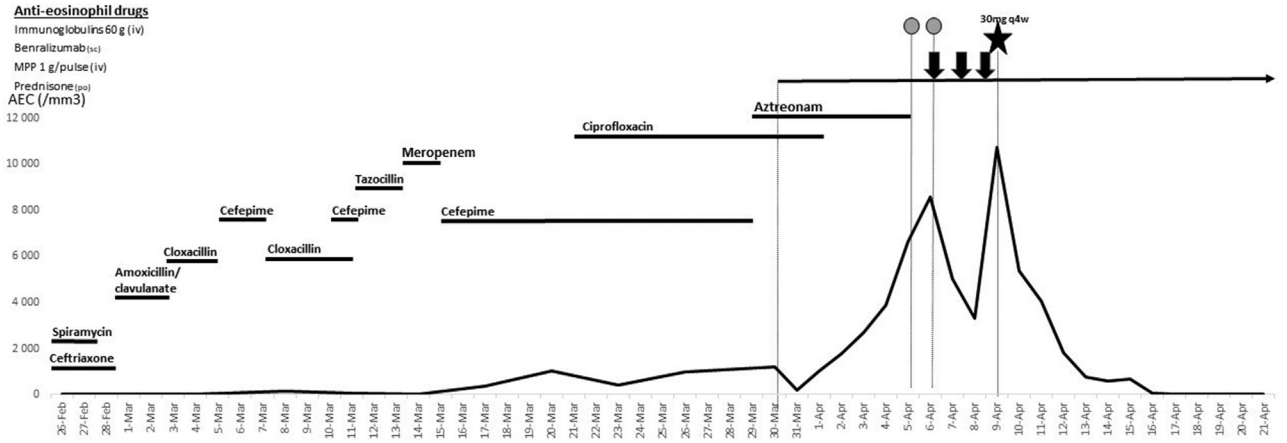

FIGURE 1. Eosinophilia evolution, specific management, and pharmacological history of the patient in the ICU. *AEC*, Absolute eosinophil count; *IV*, intravenous; *MPP*, methylprednisolone pulses; *PO, per os* (by mouth); *SC*, subcutaneous.

prominent hypereosinophilia ($6.7 \times 10^3/mm^3$) occurring 38 days after admission in our intensive care unit (ICU) for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-related acute respiratory distress syndrome. Because the RegiSCAR score was 8 and an extensive etiological workup ruled out alternate causes, the diagnosis of "definite" DRESS complicated by multiple organ failure was retained.[2] Cefepime (prescribed for ventilator-acquired pneumonia) was the most likely culprit drug (Figure 1; see Figure E1 in this article's Online Repository at www.jaci-inpractice.org). Treatment with topical steroids, methylprednisolone pulses (2 mg/kg/d, then 1 g/d for 3 days), norepinephrine (infusion rate, up to 10 mg/h), intravenous immunoglobulins (1 g/d for 2 days), and massive crystalloid replacement was started. Although the patient's hemodynamic status stabilized, worsening eosinophilia (up to $10 \times 10^3/mm^3$) and severe hemophagocytic lymphohistiocytosis (with profound thrombocytopenia) was evidenced. Subsequently, benralizumab (30 mg subcutaneous) was started, enabling dramatic improvement in the patient's condition, with a spectacular decrease in eosinophilia within 2 days, resolution of hemophagocytic lymphohistiocytosis, and improvement in both organ dysfunction and skin lesions (Figure 1; see Figures E1 and E2 in this article's Online Repository at www.jaci-inpractice.org). The patient ultimately withdrew dialysis and was discharged from the ICU 4 weeks after benralizumab treatment. To safely taper systemic steroids, a second injection of benralizumab was given at week 4.

The pathophysiology of DRESS is not fully understood. In patients with genetic susceptibility, type IV hypersensitivity to culprit drugs leading to the overproduction of IL-5 and subsequent polyclonal eosinophilia is a key feature. Benralizumab has the ability to induce rapid sustained depletion of eosinophils in both blood and tissues.[1,3] Here, we chose to use benralizumab given prominent eosinophilia, multiple eosinophil-related organ damage, failure of both systemic steroids and immunoglobulins, and the promising results reported by Schmid-Grendelmeier et al as well as in other systemic eosinophil-related diseases. Moreover, in this critically ill immunocompromised patient, this drug seemed to have a better safety profile than cyclosporine or etoposide, which could also have been considered.[4,5]

Herpesviridae reactivation has been reported in a proportion of patients with DRESS, but in the present case, serum viral loads of human simplex virus 1, human simplex virus 2, varicella zoster virus, cytomegalovirus, Epstein-Barr virus, and human herpes virus 6 were unremarkable. Conversely, we were surprised to find evidence of viral shedding of SARS-CoV-2 in a bronchial aspiration 48 days after admission to the ICU, raising the question about a potential role of SARS-CoV-2 in the onset of DRESS, in addition to drug hypersensitivity, as hypothesized by Balconi et al.[6]

Overall, benralizumab holds promise and deserves further evaluation in critically ill patients with steroid-resistant DRESS and massive expansion of eosinophils. Further data—from both COVID-19 and non–COVID-19 settings—are warranted.

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Reply to "Benralizumab: A potential tailored treatment for life-threatening DRESS in the COVID-19 era"

To The Editor:

It is exciting to see that IL-5 receptor alpha (IL-5Rα) blockade (benralizumab) is gaining interest as a therapy for drug rash with eosinophilia and systemic symptoms (DRESS) in the setting of severe acute respiratory syndrome coronavirus 2 infection. In the most recent report by Mesli et al[1] and our previous article,[2] patients with severe acute respiratory syndrome coronavirus 2 infection had severe corticosteroid-refractory presentations of DRESS that rapidly responded to benralizumab. These observations raise intriguing questions.

First, whether and how does a severe coronavirus disease 2019 (COVID-19) course interfere with or favor DRESS development. On the one hand, it is conceivable that, as indicated by our own experimental work on COVID-19–related maculopapular drug rashes,[3] the systemic cytokine storm associated with severe COVID-19 favors hyperactivation of T cells, which in turn may predispose patients to delayed drug hypersensitivity reactions. On the other hand, DRESS onset may also precede/induce viral reactivation. The latter hypothesis is supported by (a) the virus detected in bronchial aspirates of Mesli et al's patient 48 hours after intensive care unit admission and (b) our knowledge about the occurrence of viral reactivation (eg, Human Herpes Virus 6 and Epstein-Barr Virus) in DRESS.[4]

The second important question concerns the therapeutic potential of the IL-5 axis interference in DRESS beyond the setting of COVID-19. To this end, we can now report here the treatment of 3 non-COVID-19–related patients with DRESS with anti–IL-5Rα antibody (Table I). All of them fulfilled the RegiSCAR diagnostic criteria for severe DRESS[5] and had not adequately responded to systemic high-dose glucocorticoids (GCSs). Two patients showed a rapid and complete clinical recovery (defined as regression of cutaneous/systemic symptoms and eosinophilia) from DRESS following a single administration of benralizumab and concurrent tapering of low-dose GCSs. The third patient had a long relapsing course of DRESS before starting benralizumab and developed a clinical relapse and eosinophilia 4 months after the injection. We therefore decided to treat her with mepolizumab every 4 weeks (so far administered twice), and she became and has remained symptom-free.

These additional findings argue in favor of IL-5 axis blockade as a broader therapeutic option in DRESS, possibly associated with less adverse effects when compared with GCSs and other "classical" systemic immunosuppressants. To further implement this therapeutic approach in DRESS, several aspects need to be addressed: do only certain subgroups of patients benefit from IL-5 axis blockade (eg, patients with severe DRESS or those with evidence of viral reactivation); will IL-5 blockade have similar efficacy to targeting IL-5Rα or should a combination be considered; do patients require single or multiple administrations of the drug; and should patients receive coadministration of GCSs or topical corticosteroids?

Taken together, there remains a great need for prospective studies of therapeutic agents interfering with the IL-5 axis in DRESS and investigations exploring the pathomechanisms underlying DRESS within or unrelated to COVID-19.

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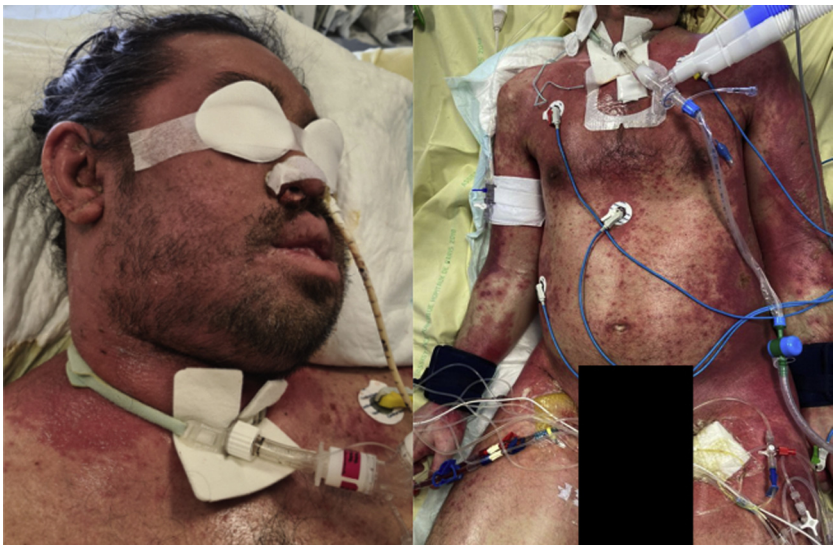

FIGURE E1. Skin rash on April 5: diffuse purpuric lesions extend approximately on 70% of the body surface area, including the ears with severe skin infiltration and facial edema.

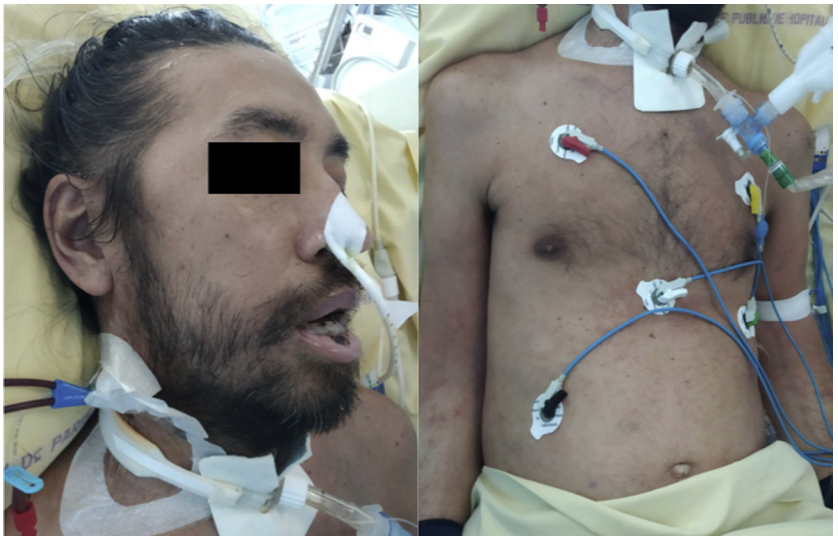

FIGURE E2. Skin evolution on April 21: Improvement with complete regression of the facial edema and purpuric lesions, persistence of a discreet postinflammatory hyperpigmentation on the upper limbs and trunk.