such as SCF, IL-3, IL-5, TNFα, PGD2, and tryptase, which enhance the activation status of both cells.4,5

This interaction has therefore short- and long-term proinflammatory effects on both cells. On MCs, the crosstalk induces tryptase and β-hexosaminidase release and Lyn and Syk phosphorylation within 1 to 2 hours after MC-Eos engagement.6 On Eos, it causes eosinophil peroxidase release, LAMP-1 expression, and chemotaxis from 1 to 3 hours after the interaction begins.5 Remarkably, both cells present with augmented TNFα and GM-CSF release and prolonged survival 1 to 7 days after initiation of the crosstalk, highlighting the role of the AEU in perpetuating allergic inflammation.4,6 The AEU might account for the persistence of lung symptoms after omalizumab administration, possibly by its prominent role in the lungs rather than IgE-dependent MC activation.

The authors propose that the MC-Eos interactions might involve receptors such as Siglec-7 and Siglec-8, which were described, together with CD300a, as inhibitory receptors (IRs) on both cells.6-9 Although it is reasonable to think that IRs might also participate in modulating the AEU, because the involved cells do express the respective ligands, for example, sialoglycans for Siglecs6,9 and phosphatidylethanolamine/phosphatidylserine for CD300a,10 in the time frame we analyzed we did not detect any inhibition of functionality of MCs or Eos ascribable to IR activation.

The novelty of the communication, together with the important clinical result, is that the AEU, mostly studied in vitro, appears to be a central component in allergic and nonallergic human diseases. In light of our reports and the evidence provided by the authors, mepolizumab might influence the course of MC-related diseases due to the formation of the AEU in the inflammation sites. However, more studies are required to unravel the effectiveness of anti-Eos compounds in diseases involving MC activation due to a concomitant tissue eosinophilia.

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Reply to “The allergic effector unit: From basic science to drug-targetable mast cell–eosinophil interactions in patients”

To the Editor:
We thank Puzzovio and Levi-Schaffer for their interest in our article.7 “Eosinophil-mast cell interaction: mepolizumab leads to a reduction of clinical symptoms and serum tryptase in a patient with eosinophilic asthma and idiopathic mast cell activation,” and their commentary on potential pathogenetic mechanisms leading to the reduction of symptoms and serum tryptase levels.7 They highlight multiple interesting potential interaction mechanisms between mast cells and eosinophils, leading to the immediate and long-lasting response to treatment with mepolizumab in our patient with idiopathic mast cell activation syndrome.

The authors themselves have extensive experience in studying eosinophil–mast cell interactions. They point out the importance of the allergic effector unit (AEU) and potential mechanisms of interaction between eosinophils and mast cells, namely the reduced secretion of IL-9 by eosinophils after mepolizumab treatment,7 direct physical crosstalk,4 and bidirectional activation via release of soluble mediators.7 Potential mechanisms of interaction are summarized in Figure 1.5-6

Recent observations suggest that eosinophils might contribute to the perpetuation of chronic mast cell–driven diseases. For example, in chronic spontaneous urticaria (CSU), elevated counts of infiltrating eosinophils have been observed in the lesional patient skin but not in the uninvolved skin.6 In addition, low counts of peripheral blood eosinophils or even the complete absence of eosinophils in patients with CSU (ie, eosinopenia) is associated with higher disease activity, type IIb autoimmunity, and a poorer response to treatment.6 Successful treatment of CSU with mepolizumab or another IL-5 receptor targeting monoclonal antibodies has been reported in case reports and case series, and clinical trials are currently performed and evaluated.
(NCT03494881, NCT03183024). In systemic mastocytosis (SM), an abundance of eosinophils is considered as a negative prognostic factor and, to our knowledge, targeting eosinophils for symptom control in SM has not yet been evaluated in clinical practice.

Interestingly, it has recently been shown that the expression level of eosinophil and mast cell mediators are increased in patients with COVID-19. This finding also implies that the AEU is not only driving allergic but also nonallergic inflammatory conditions.

In conclusion, pharmacological targeting of eosinophils might effectively reduce mast cell activity and thereby potentially prevent sometimes severe symptoms in mast cell–driven diseases. Thus, this therapeutic concept should be further explored.

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The safety and efficacy of direct oral challenge in trimethoprim-sulfa methoxazole antibiotic allergy

To the Editor:

In “Oral challenge with trimethoprim-sulfamethoxazole in patients with ‘sulfa’ antibiotic allergy,” Krantz et al1 present data supporting the safety and efficacy of direct oral challenge for low-risk sulfa antibiotic allergy in predominantly non–HIV infected patients. They demonstrated that 191 of 204 patients (94%) were successfully challenged with trimethoprim-sulfamethoxazole (Co-T). Although this introduced an important alternative to traditional assessment for commonly reported sulfa antibiotic allergy, international prospective validation of this and similar protocols, especially in the HIV negative–immunocompromised population, is lacking.

Concerns regarding the reliability of skin testing have led to a focus on drug avoidance or desensitization to manage Co-T allergy. However, desensitization protocols have similar rates of immune-mediated adverse events compared with full-dose challenge in HIV infection, and negative skin testing may indicate a waning of Co-T allergy similar to that seen with penicillins. This supports allergy reassessment as standard of care in immunocompromised patients and suggests that direct oral Co-T challenge may be a safe and effective alternative to desensitization.

All adult patients referred to antibiotic allergy services (Austin Health and Peter MacCallum Cancer Centre, Victoria, Australia) were assessed prospectively using a standardized method, and recorded in a database. In line with Krantz et al, patients with a nonsevere (ie, excluding severe cutaneous adverse reactions


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