

presenting signs of drug allergy and therefore it is imperative that the dermatologist can classify these drug allergy reaction patterns to characterize the clinical prognosis and consider the appropriate therapeutic options.

So how do clinicians tell the difference between severe drug hypersensitivity reactions and those that are likely to follow a benign course? For IgE-mediated reactions, evolution of urticaria and angio-oedema into anaphylaxis is usually straightforward to recognize and implement appropriate management. The delayed-hypersensitivity reactions are thought to be T-cell mediated and the most severe are Stevens–Johnson syndrome and toxic epidermal necrolysis (TEN). TEN has a mortality of about 25–35%³ and is characterized by a systemic illness with the presence of severe mucosal and cutaneous blistering. Most cases of TEN have distinctive clinical signs and dermatologists can readily make the diagnosis. However, other potentially dangerous drug reactions can be harder to classify from the clinical appearance alone.

One such pattern of drug hypersensitivity has had multiple names over the years and is now widely known as drug reaction with eosinophilia and systemic symptoms (DRESS), which represents approximately 4% of all drug allergy reactions with cutaneous signs. DRESS was characterized by Bocquet *et al.* in 1996⁴ and has a reported mortality of 5–10%.⁵ DRESS cases are known to exhibit a variety of different rashes that can be indistinguishable from those seen in benign drug-induced exanthems, but DRESS is distinguished by the presence of fever, lymphadenopathy, blood count abnormalities and organ dysfunction. In the review of 27 cases of DRESS reported by Walsh *et al.*⁶ in this issue of *BJD*, further subclassification on the basis of cutaneous features was shown to offer prognostic significance. The authors noted that patients with DRESS presenting with an erythema multiforme (EM)-like eruption (purpura and atypical targets) showed significantly greater elevation of liver enzymes ($P = 0.01$) and, in their series, two out of eight patients with EM-like DRESS died vs. one of 19 cases of non-EM-like DRESS. Replication of these findings in other cohorts will be necessary. However, this report suggests that beyond making the diagnosis of DRESS, identification of EM-like DRESS is an important clinical finding. Further work will be required to address whether any intervention in EM-like DRESS (e.g. with glucocorticoids) should be earlier or more aggressive, but it would seem appropriate to enhance the monitoring of such cases with specific lookout for severe hepatic dysfunction.

Conflicts of interest

None declared.

¹Clinical and Experimental Sciences, Faculty of Medicine, Sir Henry Wellcome Laboratories, University of Southampton, Mailpoint 825, Level F, South Block, Southampton SO16 6YD, U.K.

²University Hospital Southampton NHS

M.R. ARDERN-JONES^{1,2}

Foundation Trust, Southampton General Hospital, Southampton SO16 6YD, U.K.

E-mail: m.aj@soton.ac.uk

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The effects of pimecrolimus on the innate immune response in atopic dermatitis

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Understanding how topical therapies for atopic dermatitis (AD) have positive and negative effects on all aspects of the disease process is important for designing optimal treatment regimens. The letter by Afshar *et al.* in this issue of *BJD* gives important insights regarding the effects of topical calcineurin inhibitors (TCI) on the innate immune system, which is very important in defending against *Staphylococcus aureus*.¹

The skin of patients with AD is highly susceptible to colonization by *S. aureus*, a potentially pathogenic microorganism associated with the increased severity and persistence of the condition.² More than 90% of skin lesions harbour *S. aureus*, often in excess of one million organisms per cm².³ Although *S. aureus* displays preferential binding at inflamed skin sites, normal-appearing skin can also be colonized.⁴ The increased susceptibility of the skin to *S. aureus* colonization results from elevated stratum corneum pH and an abnormal innate immune response.⁵ In AD there is an acquired inability to induce sufficient levels of active antimicrobial peptides (AMP), including cathelicidin (LL-37) and human β -defensin (hBD)-3, in response to challenge.^{6,7} The level of LL-37 expressed in AD lesions is inversely related to the severity of the condition.⁸ Moreover, a deficiency of LL-37 predisposes to eczema herpeticum.⁹ The severity and progression of AD is also closely linked to the expression of the T helper 2 cytokine, interleukin (IL)-13.¹⁰ Elevated levels of IL-13 in AD lesions are thought to suppress the innate immune system, by inhibiting LL-37 and

hBD-3 expression, and facilitate changes in stratum corneum pH via suppression of flaggrin expression.^{5,7,11} Inhibiting the expression of IL-13, and promoting the expression of AMPs, is therefore an important novel approach for treating AD.

In a previous *in vitro* study, a series of calcineurin inhibitors were found to promote the expression of LL-37 and hBD-3 by keratinocytes in response to bacterial stimuli.¹² Importantly, this effect was additive to the positive effect of vitamin D on their expression. Both oral vitamin D supplementation and the use of TCIs are associated with improvement of AD symptoms; however, the mechanisms are not wholly understood.^{13,14} This interesting study conducted by Afshar *et al.*¹ investigated the effect of the TCI pimecrolimus on IL-13 and AMP expression *in vivo* in patients with AD.

The application of pimecrolimus to AD lesional skin for 3 weeks significantly reduced hBD-3 and had no effect on LL-37 mRNA expression. The results fit well with another similar study, which investigated the effect of pimecrolimus on protein expression of a number of AMPs.¹⁵ Pimecrolimus treatment appeared to reduce the elevated levels of AMPs associated with inflammation back to just under the level of expression observed in healthy skin. Topical corticosteroids (TCS) were associated with a more pronounced inhibition of AMP protein and mRNA levels, suggesting a greater suppression of the innate immune system. The striking disparity between the existing *in vitro* and *in vivo* findings may result from the changes brought about by inflammation, and highlight the need for more *in vivo* studies such as this one.

Importantly, pimecrolimus was found to inhibit the expression of IL-13. In addition to its association with the innate immune system, IL-13 plays a pivotal role in the development of acute AD lesions, and via thymic stromal lymphopoietin appears to promote progression to other atopic conditions such as asthma.¹⁰ In view of the limitations of, and sometimes not clinically relevant results from, *in vitro* experiments, further *in vivo* research is required better to understand how TCIs, including pimecrolimus and tacrolimus, and TCS affect the innate immune system and skin barrier function. Through this research the best method to combine these treatments in the short- and long-term management of AD can be determined.

Conflicts of interest

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¹Academic Unit of Dermatology Research,
Department of Infection and Immunity,
Faculty of Medicine, Dentistry and Health,
University of Sheffield Medical School,
Beech Hill Road, Sheffield S10 2RX, U.K.

S.G. DANBY¹
M.J. CORK^{1,2,3}

²Department of Dermatology,
Royal Hallamshire Hospital,
Sheffield Teaching Hospitals Trust, Sheffield, U.K.

³Paediatric Dermatology Clinic,
Sheffield Children's Hospital, Sheffield, U.K.

Correspondence: Michael J Cork

E-mail: m.j.cork@sheffield.ac.uk

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