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Increased healthcare costs for filaggrin-related eczema and asthma: hope for targeted management and prevention

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Linked Article: Soares et al. *Br J Dermatol* 2018; **179**:717–723.

In this issue of the *BJD*, Soares et al.¹ report on whether *FLG* mutations were associated with increased prescribing for eczema and asthma in Scotland. Filaggrin is essential for the terminal differentiation of keratinocytes and the formation of the stratum corneum. Furthermore, the terminal degradation products of filaggrin are thought to be an important natural moisturizing factor in the stratum corneum. Thus, a deficiency of filaggrin leads to skin-barrier defects. Epicutaneous antigens are strong sensitizers of allergic disorders, and induction of allergic diseases through epicutaneous sensitization may enhance skin-barrier disruption. Indeed, mutations in *FLG* (the gene encoding profilaggrin/filaggrin) are a significant predisposing factor for both atopic eczema and asthma across the world.^{1,2} The relationship between *FLG* mutations and allergic disorders is complex; for instance, previous studies show that *FLG* mutations are associated with patients with both eczema and asthma, but not with patients who only have asthma.^{1,3}

In the U.K., both eczema and asthma are common chronic diseases: eczema affects 2–10% of adults and 15–20% of children, while asthma affects 16–18% of the U.K. population.¹ More than 50% of individuals with eczema will develop asthma and/or another allergic disease in their lifetime.¹ As these diseases are relatively prevalent, related healthcare costs are significant. Each year the National Health Service spends

£465 million on treating eczema and £1.1 billion on treating asthma.^{4,5} Examining the relationship between the risk factors, prevalence and costs of these diseases should therefore be a priority.

Until published by Soares et al.,¹ the association between filaggrin-related eczema and/or asthma and increased healthcare costs had not been adequately examined. Soares et al.¹ report that *FLG* mutations are strongly associated with prescribing of emollients, treatment for severe eczema and a combination of long-acting β_2 -agonist and corticosteroids, and are also associated with increased prescribing for mild and moderate eczema, asthma-reliever medicine and asthma exacerbations.¹ They conclude that the presence of *FLG* mutations is associated with increased prescribing for eczema and asthma.

In order to lower the healthcare burden associated with filaggrin-related eczema and asthma in the community, interventions aimed at preventing filaggrin-related eczema and asthma should be the main priority. Recent clinical studies demonstrate that daily application of emollients to high-risk neonates can reduce the occurrence rate of atopic eczema.^{6,7} Conversely, carriers of the *FLG* mutation are not always affected with eczema or asthma, further complicating the matter.⁸

What is clear is that both clinical and economic research is required in this important topic area, and other areas of dermatology.^{9,10} The study published by Soares et al.¹ sets an important precedent in examining the burden of diseases associated with *FLG* mutations on healthcare services. We conclude that precision medicine and targeted management for filaggrin-related eczema and asthma (i.e. screening for *FLG* mutations and intensive skin care including strict emollient application to neonates with an *FLG* mutation) could potentially be an important strategy for reducing the healthcare burden associated with eczema and asthma in the U.K.

Conflicts of interest

None to declare.

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Multifocal anaplastic large cell lymphoma – insight into its biology and treatment

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Linked Article: Melchers et al. *Br J Dermatol* 2018; **179**:724–731.

Primary cutaneous anaplastic large cell lymphoma (C-ALCL) presents in most patients with a solitary tumour or grouped nodules in one anatomic region. Despite the highly atypical cytomorphology of the CD30⁺ tumour cells and the rapid tumour growth, C-ALCL has a favourable prognosis with a 5-year-survival rate between 76% to 96%.^{1–3} Surgical excision and/or radiotherapy are effective therapies and have been listed as first-line approaches in international guidelines for the management of cutaneous CD30⁺ lymphoproliferative disorders.^{4,5} In some patients C-ALCL occurs in a multifocal form with multiple nodules. The data on the course and response to treatment in multifocal C-ALCL are sparse. In addition, the recommendations for treatment in this patient group were based only on expert opinion, but data of larger studies were lacking.

This issue of the *BJD* includes an important study by Melchers et al. on the largest cohort of patients with this condition reported to date; they provide important data as a scientific basis for treatment recommendations in multifocal C-ALCL.⁶ In their study on 35 patients the authors show that radiotherapy represents an efficient and practical approach for patients with less than five tumour lesions. In patients with more than five tumours, the authors employed low-dose methotrexate (MTX) for most of their patients in

analogy to the beneficial effects of MTX in lymphomatoid papulosis, which also belongs to the group of cutaneous CD30⁺ lymphoproliferative disorders. An overall response rate of 57% was found during maintenance therapy with low-dose MTX (10–25 mg per week) and 43% of patients experienced complete remission. These data clearly demonstrate that low-dose MTX is an effective and safe treatment approach for multifocal C-ALCL. MTX is a drug that has been used for a long time for various dermatological conditions. Even when prescribed for long-term maintenance treatment over months and years, low-dose MTX is usually well tolerated and has relatively few side-effects.

In addition to the aspects on the efficacy of MTX in C-ALCL, the study also revealed additional interesting results as four patients with multifocal C-ALCL experienced spontaneous complete regression of all tumour lesions within a period of 4 to 20 weeks without any treatment. Thus, a wait-and-see strategy for 4 to 6 weeks may be justified in some rare instances, especially in patients with multiple papular and slowly growing tumoral lesions. On the other hand, extracutaneous spread and fatal outcome was more frequently observed in patients with multifocal C-ALCL who presented with more than five tumour lesions. Furthermore, the data corroborate previous studies demonstrating that multiagent chemotherapy is not indicated for multifocal C-ALCL limited to the skin as all patients experienced relapses during follow-up after multiagent chemotherapy.

Alternative therapeutic approaches are still needed, as not all patients with multifocal C-ALCL show a response to MTX. Anti-CD30-antibody based treatment modalities such as the drug brentuximab vedotin (BV), a CD30 antibody-drug conjugate composed of the cytotoxic antitubulin agent monomethyl auristatin E, are ideal candidates for multifocal C-ALCL, as CD30 is preferentially expressed on tumour cells and only in a very limited extent on a small subset of normal cells. In a recent international, open-label, randomized phase III multicentre trial of BV (1.8 mg kg⁻¹ once every 3 weeks) (the ALCANZA study) in primary cutaneous CD30⁺ lymphoproliferative disorder, the overall response rate lasting at least 4 months was 75% (12 of 16 patients) in the C-ALCL group that included patients with multifocal presentation in addition to those with extracutaneous involvement.⁷ Out of those, five patients had a complete response to BV with a median duration of complete response of 17 weeks. The use of BV, however, is limited by sensory peripheral neuropathy, which represents a major and potentially irreversible adverse effect developing in more than half of the patients. Treatment with BV at lower doses and/or at longer intervals may decrease the risk for peripheral neuropathy without resulting in loss of therapeutic efficacy, but the best dose regimens have still to be determined.⁸

In conclusion, the data by Melchers and coworkers provide the rationale to treat patients with multifocal C-ALCL presenting with more than five tumours with low-dose MTX as