

Schering-Plough, Takeda, Teva, UCB Pharma, VBL therapeutics, Wyeth Pharma.

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Supporting Information

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Ustekinumab for severe atopic dermatitis: an important negative study

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Linked Article: Sacki et al. *Br J Dermatol* 2017; **177**:419–427.

Atopic dermatitis (AD) is a common chronic inflammatory skin disease characterized by pruritus, eczematous lesions and xerosis that has a substantial impact on patients' quality of life. The vast majority of cases are managed in general practice and although often appropriately managed using topical moisturizers and steroid ointment/creams, referral to dermatology is required when disease becomes refractory to simple topical treatment.¹ Systemic nonbiologic drugs such as azathioprine, methotrexate and ciclosporin are among the options available to dermatologists but response is variable and these medications have substantial side-effect profiles.²

The pathophysiology of AD is a complex interaction of susceptible genes, environmental triggers, impaired skin barrier and dysregulated immune response. As our understanding of the molecular pathways involved in AD improves, so does the potential use of targeted biologic therapies that target key molecules in these various pathways.³

Dupilumab, a monoclonal antibody against interleukin (IL)-4 receptor α , has shown promising results at reducing pruritus, skin lesions and quality of life for patients with AD and was licensed by the U.S. Food and Drug Administration in March 2017.⁴ However, response to treatment was not universal among trial participants and suggests variance in the key molecular mechanisms and immunological mechanisms that are driving their disease. Omalizumab and rituximab have shown mixed results in case series and reports for the treatment of AD and so far no other targeted therapies have had the same success in AD.^{5–8}

Ustekinumab is licensed for the treatment of moderate-to-severe psoriasis and modulates T-helper (Th)1, Th17 and Th22 activation. Th cells are categorized in Th subsets according to their production of lineage-indicating cytokines and functions. Th17 cells represent one subset that produces, among other cytokines, IL-17 and IL-22.⁹ There is a suggestion that Th17 cells may be involved in this pathogenesis of AD.¹⁰

Earlier this year an American study found no significant improvement in AD from ustekinumab compared with placebo in a phase II randomized, double-blind, placebo-controlled, crossover-designed trial.¹¹ However, it was noted that clinical outcomes may have been obscured by a profound 'placebo effect'. Participants received subcutaneous ustekinumab (45 or 90 mg for patients weighing ≤ 100 or > 100 kg, respectively) or placebo at weeks 0, 4 and 16 with a crossover to the other agent (either ustekinumab or placebo) at weeks 16, 20 and 32. Although mean reduction in SCORAD

(atopic dermatitis severity-scoring tool for atopic dermatitis) from baseline to week 40 was significant for both groups, SCORAD50 (a reduction of $\geq 50\%$ in total score) was not statistically different between the groups at either 16 or 32 weeks.

In the current issue of the *BJD*, Saeiki *et al.*¹² report the results of a phase II study examining the efficacy and safety of ustekinumab in Japanese patients with severe AD. Patients were randomized to one of three groups: 45 mg ustekinumab, 90 mg ustekinumab (independent of their weight) or placebo. This study did not demonstrate any meaningful efficacy (or trend) for primary or secondary endpoints compared with placebo in patients with severe AD but ustekinumab was generally well tolerated. However, both the active and the placebo groups showed a mean improvement of $\sim 38\text{--}40\%$ (with wide confidence intervals) in Eczema Area and Severity Index (EASI) scores at 12 weeks. The authors suggest that background use of potent topical corticosteroids and calcineurin inhibitors improved compliance to concomitant medications and the psychological effect of receiving injections may have masked potential differences.

The results of this study are doubly disappointing as the typical Asian AD phenotype appears more 'Th17 driven' than other forms of AD and it had been hoped that ustekinumab might work better in these patients.¹³ The rate of filaggrin variants was lower than reported in European and U.S. studies and the small number of patients with filaggrin variants precluded meaningful analysis. Nevertheless, stratification according to filaggrin status should be explored in future larger-scale studies, particularly as it has been shown that omalizumab, another targeted therapy, had increased efficacy in wild-type filaggrin mutations.⁸ It is not entirely clear why the primary end point, defined as a 30% change in EASI score in ustekinumab compared with placebo, was chosen. This is a large change (compared with the minimal clinically important difference) and with the power calculation it is possible (although it seems unlikely from the data) that a relevant difference may have been missed.¹⁴

Overall, this was a well-conducted small study with an important negative result. In order to understand the potential efficacy and properties of future targeted therapies and their impact on AD pathogenesis, future studies may need to be conducted without the confounding effects of moderate-strength topical corticosteroids. It could be argued that the placebo effect reported from these and other studies demonstrates the impact of adherence to standard topical corticosteroid therapy and concomitant medications can have on AD.¹⁵

Psoriasis, a disease with a similarly complex pathophysiology, is a perfect example of how an improved understanding of molecular pathways can lead to targeted therapies for a chronic skin condition that has revolutionized treatment. Thus, although tumour necrosis factor inhibitors were first utilized in inflammatory arthritis and subsequently psoriasis, the introduction of ustekinumab and anti-IL-17 agents (e.g. secukinumab), which are now used routinely in the U.K. for the

treatment of refractory psoriasis, was based on an increased understanding of psoriasis pathophysiology. Additionally, certain forms of psoriasis (such as pustular psoriasis) show distinct genetic and molecular signatures and are resistant to conventional psoriasis therapy, and trials of novel agents such as anakinra are currently underway.¹⁶ Unfortunately, in refractory atopic eczema the repertoire of targeted systemic and biological therapies remains limited at present. Therefore, further studies are required to increase understanding about the complex interrelationship between epidermal barrier dysfunction, filaggrin variant status and the inflammatory/immune pathways that are activated and amenable to therapeutic intervention in AD.

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Conflicts of interest

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The role of access to care in acral lentiginous melanoma survival

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Acral lentiginous melanoma (ALM) is poorly understood, and given its low incidence,¹ very little has been reported on this topic. Acral melanomas are thought to have a worse prognosis than cutaneous malignant melanomas overall,^{2,3} so a better understanding of the impact of demographic and clinical factors on ALM outcome is crucial.

In this issue of the *BJD*, Asgari and colleagues present the results of a retrospective study of patients diagnosed with ALM by Kaiser Permanente Northern California (KPNC).⁴ By using only insured patients from an integrated healthcare delivery system, the authors attempt to reveal the role of healthcare access in ALM-specific survival.

A cohort of 123 consecutive KPNC members diagnosed with ALM between 1987 and 2013 were analysed with respect to

patient and tumour characteristics, and their clinical management. Univariate and multivariate Cox regression models were used to estimate unadjusted and adjusted hazard ratios (HRs and aHRs) for all-cause and melanoma-specific mortality.

In univariate models, the authors found that older age was not associated with melanoma-specific survival. Although males tended to have higher aHRs for all outcomes, there was no statistically significant association between sex and overall or melanoma-specific survival. Additionally, decreased melanoma-specific survival was associated with Breslow depth > 2 mm, presence of ulceration, and extent of disease. When adjusted for age, sex, Breslow thickness and extent of disease, there was no survival difference by race-ethnicity.

Although some studies have shown that minority groups have worse melanoma outcomes,⁵ others have demonstrated that survival rates are actually similar among racial-ethnic groups if controlled for thickness and stage, which tend to be thicker and later in minorities.^{1,6,7} Importantly, Asgari et al.⁴ conclude that cancer survival differences previously noted between whites and nonwhites may result from barriers to healthcare access rather than disease biology. This is a significant explanation that warrants further investigation.

Unfortunately, only 5 blacks, 11 Hispanic whites and 13 Asians were included in the nonwhite cohort, limiting the power of this analysis. The small sample size also raises questions of generalizability. Blacks in this study made up only 4.1% of the total ALM cases, compared with 9.2% of a U.S. population-based ALM analysis; and Asians/Pacific Islanders made up 11%, compared with 5.9%.¹ Additionally, only 11% of tumours were diagnosed at thicker than 2.00 mm, compared with 37% in the population-based study. These discrepancies potentially reflect a suboptimal representation of national patient and tumour characteristics. In the future, collaborative, multicentre research may be needed to increase sample size and improve generalizability.

Lastly, while a contained healthcare system is a unique resource in which to examine uniform access to care, it has been shown that even when racial-ethnic minorities have the same access to healthcare, the quality of their care may not be equivalent to that of other groups – due to patient preferences and behaviours, differential treatment by providers, and socioeconomic factors.⁸ Future, larger studies that take into account Breslow thickness and disease stage, in addition to access to care, could further elucidate the relationship between race-ethnicity, delayed diagnosis and melanoma-specific mortality.

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Conflicts of interest

None to declare.