2 Wiegell SR, Haedersdal M, Philipsen PA *et al*. Continuous activation of PpIX by daylight is as effective as and less painful than conventional photodynamic therapy for actinic keratoses; a randomized, controlled, single-blinded study. *Br J Dermatol* 2008; **158**:740–6.
3 Wiegell SR, Fabricius S, Heydenreich J *et al*. Weather conditions and daylight-mediated photodynamic therapy: protoporphyrin IX-weighted daylight doses measured in six geographical locations. *Br J Dermatol* 2013; **168**:186–91.
4 Mordon S, Vignion-Dewalle AS, Abi-Rached H *et al*. The conventional protocol vs. a protocol including illumination with a fabric-based biophotonic device (the Phosistos protocol) in photodynamic therapy for actinic keratosis: a randomized, controlled, noninferiority clinical study. *Br J Dermatol* 2020; **182**:76–84.
5 Rioli DI, Samimi M, Beneton N *et al*. Efficacy and tolerance of photodynamic therapy for vulvar Paget's disease: a multicentric retrospective study. *Eur J Dermatol* 2018; **28**:351–5.

Dupilumab in adolescent atopic dermatitis: interpreting the data

DOI: 10.1111/bjd.18627

Linked Article: Cork *et al*. *Br J Dermatol* 2020; **182**:85–96.

Dupilumab, a fully human IgG4 monoclonal antibody blocking interleukin (IL)-4 and IL-13, has rapidly established itself as a first-line therapy in adults with severe atopic dermatitis, demonstrating significant efficacy without the immunosuppressive effects of other systemic medications.[1] These features highlight its appeal for treatment in children where current systemic therapies include ciclosporin and methotrexate.[2,3]

In this issue, Cork *et al* presents the initial industry-sponsored paediatric data for dupilumab.[4] In the phase IIa study, 40 adolescents aged 12–17 years received dupilumab 2 mg kg^{-1} or 4 mg kg^{-1}, with monitoring over 8 weeks, followed by 4 weekly doses and another 8 weeks of monitoring. Results confirmed target serum concentrations within 1 week of initial doses, increased serum concentrations correlating with increased doses and nonlinear elimination pharmacokinetics. Thirty-six patients then continued weekly doses with optional concurrent topical therapy for 52 weeks. Improvement via an Investigator's Global Assessment of 0 or 1 was reported in 10% and 35% of patients at 12 weeks with doses of 2 mg kg^{-1} and 4 mg kg^{-1}, respectively, and 38% and 44% at 52 weeks. Side-effects included conjunctivitis (18% and 16%), skin infections (29% and 42%) and injection-site reactions (18% and 11%) with 2 mg kg^{-1} and 4 mg kg^{-1} dosing, respectively.

Important caveats need to be considered. The weekly individual weight-based doses contrast with the approved regimen of 400 mg or 600 mg followed by bi-weekly doses according to weight category (200 mg or 300 mg). As a result, most participants were exposed to higher overall amounts of drug, and the data represents a more important reference for short-term safety than efficacy. The lack of placebo arm and concurrent topical medications also limit the ability to interpret efficacy data, given benefits noted with topical monotherapy in prior studies.[5]

Conjunctivitis is a now well-recognized anticipated side-effect of dupilumab, occurring more commonly in the atopic dermatitis population.[6] Many theories about its pathogenesis exist, with goblet cell and mucin production decrease possibly implicated.[7] Current recommendations include ophthalmologist referral, elimination of eye rubbing, cold compresses, avoidance of exacerbating factors and artificial tears.[8]

Although skin infections were more common in study participants receiving higher dupilumab doses, adult studies have reported increased infections in untreated patients, and more paediatric data is clearly needed to understand dupilumab's full effects on infection risk.[1] Injection-site reactions were mild, but needle phobia may need to be addressed in adolescents, which can be mitigated with psychosocial strategies.[9] Another consideration is the need of concurrent vaccination, which was not allowed in this study. However, promising adult data has shown no impact of dupilumab on the efficacy of both T-cell dependent and independent inactive vaccines.[10]

As with any new therapy, registry data and diligent reporting of possible treatment-related adverse effects will be important moving forward to detect safety concerns. Assessment of disease severity, impact on quality of life, and pre-existing comorbidities at baseline and during therapy will allow better interpretation of any events in patients.

Irrespective of other therapies on the horizon,[11] dupilumab will likely become a cornerstone of treatment for children with moderate-to-severe atopic dermatitis, and it is therefore important for clinicians to be familiar with the pharmacokinetics and safety data from these studies.

C. Sibbald

Section of Dermatology, Department of Paediatrics, The Hospital for Sick Children, Toronto, Canada
E-mail: cathryn.sibbald@mail.utoronto.ca

References

1 Boguniewicz M, Fonacier L, Guttman-Yassky E *et al*. Atopic dermatitis yardstick: practical recommendations for an evolving therapeutic landscape. *Ann Allergy Asthma Immunol* 2018; **120**:10–22.
2 Totri CR, Eichenfield LF, Logan K *et al*. Prescribing practices for systemic agents in the treatment of severe pediatric atopic dermatitis in the US and Canada: the PeDRA TREAT survey. *J Am Acad Dermatol* 2017; **76**:281–5.
3 Proudfoot LE, Powell AM, Ayis S *et al*. The European TREatment of severe Atopic eczema in children Taskforce (TREAT) survey. *Br J Dermatol* 2013; **169**:901–9.
4 Cork MJ, Thaçi D, Eichenfield LF *et al*. Dupilumab in adolescents with uncontrolled moderate-to-severe atopic dermatitis: results

from a phase IIa open-label trial and subsequent phase III open-label extension. *Br J Dermatol* 2020; **182**:85–96.
5 Broeders JA, Ahmed Ali U, Fischer G. Systematic review and meta-analysis of randomized clinical trials (RCTs) comparing topical calcineurin inhibitors with topical corticosteroids for atopic dermatitis: a 15-year experience. *J Am Acad Dermatol* 2016; **75**:410–9.
6 Akinlade B, Guttman-Yassky E, de Bruin-Weller M *et al*. Conjunctivitis in dupilumab clinical trials. *Br J Dermatol* 2019; **181**:459–73.
7 Bakker DS, Ariens LFM, van Luijk C *et al*. Goblet cell scarcity and conjunctival inflammation during treatment with dupilumab in patients with atopic dermatitis. *Br J Dermatol* 2019; **180**:1248–9.
8 Silverberg J. Revolutionizing atopic dermatitis. *Cutis* 2019; **104**:142–3.
9 Armenta AM, Jaquez SD, Levy ML, Diaz LZ. Use of psychologic strategies to reduce pain and anxiety related to dermatology procedures. *Pediatr Dermatol* 2019; **36**:416–17.
10 Blauvelt A, Simpson EL, Tyring SK *et al*. Dupilumab does not affect correlates of vaccine-induced immunity: a randomized, placebo-controlled trial in adults with moderate-to-severe atopic dermatitis. *J Am Acad Dermatol* 2019; **80**:158–67.
11 Nguyen HL, Anderson KR, Tollefson MM. New and emerging therapies for pediatric atopic dermatitis. *Paediatr Drugs* 2019; **21**:239–60.

Funding sources: none.

Conflicts of interest: C.S. has received honoraria from RBC consultants and Novartis for work unrelated to this manuscript.

Causal inference in melanoma epidemiology using Mendelian randomization

DOI: 10.1111/bjd.18646

Linked Article: Liyanage *et al*. *Br J Dermatol* 2020; **182**:97–103.

In this issue of the *British Journal of Dermatology*, Liyanage *et al*. report a Mendelian randomization study that found no evidence of a causal association between vitamin D and melanoma.[1] Previous observational studies found positive, negative and no associations, but are limited by confounding by ultraviolet radiation exposure, skin pigmentation, and other factors that influence both vitamin D level and risk of melanoma. Mendelian randomization studies overcome some of the problems caused by unmeasured confounders and reverse causation, by using genetic variants as 'instrumental variables' to support causal inferences.[2] These studies require three key assumptions: relevance (also called 'strong instrument': genetic variants are associated with the risk factor), exclusion restriction (the effects of the genetic variants on outcome are only through the risk factor) and independence (also called 'exchangeability': there is no common cause of the genetic variants and outcome).[3]

Liyanage *et al*.[1] demonstrate evidence that the five genetic variants in the study are robustly associated with vitamin D levels, satisfying the 'relevance' assumption. They test for other possible causal pathways to melanoma (horizonal pleiotrophy) in sensitivity analyses, providing reassurance that the 'exclusion restriction' assumption may be reasonable. The genome-wide association studies used in the analysis controlled for potential confounding by ancestry (population stratification), so the 'independence' assumption may also be justified. Findings of no association between the genetic variants and a range of characteristics [analogous to balance in baseline characteristics between trial arms in a randomized controlled trial (RCT)] also supports the plausibility of the exclusion restriction and exchangeability assumptions. A possible challenge to the exclusion restriction assumption is the large measurement error in vitamin D, which may mean that not all components of the genetically determined vitamin D are captured.[4] Further, vitamin D was measured at only one time point in the primary studies, whereas genetically determined changes in vitamin D at other time points may be important, as might gene–environment interactions whereby the effect of the genetic variants is modified by environmental factors such as sun exposure.

We should also note that the finding of no causal effect in this study is for the development of melanoma, not the risk of progression or recurrence.[5] Other Mendelian randomization studies using genetic variants that are associated with melanoma recurrence would be needed to investigate that causal association. Such studies would complement findings from the RCTs of vitamin D that are currently underway in people who have been treated for melanoma.[6]

Finally, other higher-quality evidence on whether or not vitamin D is a risk factor or protective factor for melanoma may be possible through meta-analysis of RCTs of vitamin D supplementation.[7–10] One major difference, though, is that the duration of the intervention (higher vitamin D levels) differs between the study designs, with the Mendelian randomization studies reflecting lifelong exposure, and the trials usually reflecting much shorter, more recent exposures. For trials, linkage to cancer registry data on melanoma diagnoses may be needed where this was not initially collected for the primary hypothesis. While such meta-analyses may provide more definitive evidence on the effects of vitamin D supplementation, based on the current data available there is no indication that the vitamin either causes, or prevents, melanoma.

Acknowledgment: I thank Anne Cust for her helpful comments on an earlier draft of this editorial.

K.J.L. Bell

School of Public Health, The University of Sydney, Sydney, Australia
E-mail: katy.bell@sydney.edu.au