autoimmunity and CLE subtype were not significant risk factors. Patients with new-onset disease were more likely to be ANA positive at any point during follow-up (90% vs. 37%; P < 0.001). Logistic regression analysis also showed that positive ANA [odds ratio (OR) 10; p < 0.0001] was associated with prior-onset disease. Positive ANA (OR 16; P < 0.001) and younger age at the time of CLE diagnosis [OR 1.04 (per 10 year decrease); P = 0.04] were associated with new-onset disease. Accounting for differential follow-up time, survival analysis showed that ANA positivity was still associated with the development of a new-onset autoimmune disease (P = 0.002) (Fig. 1b). Notably, 30 of 86 (35%) patients who had an ANA titre < 1 : 160 at CLE diagnosis seroconverted by the end of follow-up, with 15 of 30 (50%) acquiring new-onset autoimmune diseases.

We found that patients with CLE without SLE had an elevated risk of developing comorbid autoimmune conditions throughout their lifetimes. Rates of secondary autoimmunity in our cohort were similar to those for patients with SLE. Compared with a SLE cohort from our institution, patients with CLE acquired a similar number of prior and new-onset autoimmune diseases (data not shown). Prior-onset diagnoses in patients with CLE were heterogeneous and aligned with the collection of diseases found in SLE. In contrast, new-onset autoimmune conditions were predominantly SLE, at rates similar to those found in previous reports. Finally, the frequency of all non-SLE autoimmune diseases in our cohort (21-2%) was still higher than that reported in the general population (4-5%). Finally, ANA positivity was significantly associated with prior-onset and new-onset autoimmune diseases. The limitations of this study included its retrospective design, resulting in missing data, and lack of a control group and paediatric patients, who were not seen in our clinics.

Thus, we recommend careful history taking and targeted reviews for symptoms of autoimmune disease (e.g. overt symptoms of thyroid disease and sicca symptoms), especially in patients with CLE and ANA positivity. For patients with CLE and an initially negative ANA, periodic repeat testing may be important in assessing the risk of developing additional autoimmunity.

Acknowledgments: we thank Rebecca Vasquez, Andrew Kim, Daniel Grabell, Noelle Teske, Tina Vinoya, Jack O’Brien, Danielle Lin, Jenny Raman and Justin Raman for recruiting patients. We thank Dr Arash Mostaghimi for his critical review of this manuscript, and Rose Cannon for help with the submission of this manuscript. We thank participants of the University of Texas Southwestern CLE Registry for their contributions to lupus research.

K.Y. Shi, E. Kunzler, L.S. Hynan and B.F. Chong
University of Texas Southwestern Medical Center, Department of Dermatology and Department of Population and Data Sciences and Psychiatry, Dallas, TX, U.S.A.
Correspondence: Benjamin F. Chong.
E-mail: ben.chong@utsouthwestern.edu

References
1 McDonagh JE, Isenberg DA. Development of additional autoimmune diseases in a population of patients with systemic lupus erythematosus. Ann Rheum Dis 2000; 59:230–2.
2 Chambers SA, Charman SC, Rahman A, Isenberg DA. Development of additional autoimmune diseases in a multiethnic cohort of patients with systemic lupus erythematosus with reference to damage and mortality. Ann Rheum Dis 2007; 66:1173–7.
3 Kunzler E, Hynan LS, Chong BF. Autoimmune diseases in patients with cutaneous lupus erythematosus. JAMA Dermatol 2018; 154:712–16.
4 Petri M, Orbai AM, Alarcon GS et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum 2012; 64:3677–86.
5 Hayter SM, Cook MC. Updated assessment of the prevalence, spectrum and case definition of autoimmune disease. Autoimmun Rev 2012; 11:754–65.
6 Ables AM, Ables M. The clinical utility of a positive antinuclear antibody test result. Am J Med 2013; 126:342–8.
7 Durosaro O, Davis MD, Reed KB, Rohlinger AL. Incidence of cutaneous lupus erythematosus, 1965–2005: a population-based study. Arch Dermatol 2009; 145:249–53.
8 Gronhagen CM, Fored CM, Granath F, Nyberg F. Cutaneous lupus erythematosus and the association with systemic lupus erythematosus: a population-based cohort of 1088 patients in Sweden. Br J Dermatol 2011; 164:1335–41.

Funding sources: this study was supported, in part, by the National Institute of Arthritis and Musculoskeletal and Skin Diseases of the National Institutes of Health under Award Number K23AR061441; the Rheumatology Research Foundation Career Development R Bridge Funding Award; and by the National Center for Advancing Translation Sciences of the National Institutes of Health under Award Number UL1TR001105. The content is solely the responsibility of the authors and does not necessarily represent the official views of the University of Texas Southwestern Medical Center at Dallas and its affiliated academic and healthcare centres, the National Center for Research Resources and the National Institutes of Health.

Conflicts of interest: B.F.C. is an investigator for Daavlin Corporation, Biogen Incorporated, and Pfizer Incorporated, and has received honoraria from Viela Bio as a consultant.

Response to R. Waldman et al.: ‘Does IL-4 inhibition play a role in dupilumab-associated conjunctivitis?’

DOI: 10.1111/bjd.18808

Linked Article: Waldman et al. Br J Dermatol 2020; 182:251. Bakker et al. Br J Dermatol 2019; 180:1248–9.

DEAR EDITOR, Bakker et al. proposed that interleukin (IL)-13 inhibition-induced goblet-cell decline drives dupilumab-associated conjunctivitis in atopic dermatitis (AD). In response,
Waldman et al.\textsuperscript{2} suggested that IL-4 inhibition is essential, citing TREBLE, a randomized, 12-week, placebo-controlled, dose-ranging phase II trial of lebrikizumab (anti-IL-13 monoclonal antibody) in moderate-to-severe AD.\textsuperscript{3}

Waldman et al. stated that conjunctivitis incidence in TREBLE was a weaker signal than that observed with dupilumab. However, no dupilumab clinical trial publications were cited. Cross-trial comparisons have limited value, but if such a comparison is made, the most suitable comparator is the dupilumab phase IIb trial (AD-1021),\textsuperscript{4} which was more similar to TREBLE than dupilumab phase III trials, as both AD-1021 and TREBLE were phase II dose-ranging trials with similar sample sizes and treatment duration. In this comparison, lebrikizumab and dupilumab conjunctivitis rates were in fact similar (see Table 1).

Waldman et al.’s comparison has critical limitations. Firstly, phase II trials are insufficiently sized for adequate safety assessments. Furthermore, AD severity correlates with conjunctivitis adverse events,\textsuperscript{5} but baseline severity was lower in TREBLE\textsuperscript{3} than AD-1021 (see Table 1) or other dupilumab trials.\textsuperscript{4,5}

Additionally, Medical Dictionary for Regulatory Activities (MedDRA) coding for conjunctivitis has changed over time. ‘Conjunctivitis’ incidence in TREBLE cannot be compared with conjunctivitis data in dupilumab labelling, which reflects multiple MedDRA preferred terms derived from comprehensive signal detection and analysis in > 2000 study patients; IL-13 inhibitors have not yet undergone such analyses. Finally, Waldman et al. cite 15-8 weeks for dupilumab-associated conjunctivitis from a 12-patient case series;\textsuperscript{6} however, in TREBLE, treatment was for ≤ 12 weeks,\textsuperscript{3} likely underestimating IL-13 blockade effects.

Conjunctivitis seen in dupilumab AD trials is a complex, multifactorial phenomenon.\textsuperscript{5} In addition to IL-13-driven goblet-cell effects, epithelial barrier disruption in AD (demonstrably improved by dupilumab) also likely plays a role. Indeed, higher dupilumab serum concentrations were associated with less conjunctivitis in AD trials,\textsuperscript{7} and conjunctivitis was not an issue in asthma trials of dupilumab (very low rates, similar for dupilumab and placebo).\textsuperscript{5} Conjunctivitis usually resolves while patients are on dupilumab and is rarely treatment limiting,\textsuperscript{5} supporting the epithelial barrier role.

Waldman et al.’s evidence does not support IL-4 inhibition as a driver of conjunctivitis. Current phase II data on IL-13 blockade are too limited to discriminate potential ocular effects of IL-13 and IL-4.

Table 1 Baseline atopic dermatitis severity and conjunctivitis incidence rates in lebrikizumab phase II (TREBLE)\textsuperscript{3} and dupilumab phase IIb (AD-1021)\textsuperscript{4} randomized, placebo-controlled clinical trials

| Condition | Baseline EASI (mean, SD) | Conjunctivitis,\textsuperscript{a} n1/N (%) |
|-----------|--------------------------|--------------------------------------------|
| TREBLE (lebrikizumab phase II)\textsuperscript{3} | | |
| Lebrikizumab 125 mg | 24-6 (11-1) | 7/54 (13) |
| single dose + TCS (n = 52) | | |
| Lebrikizumab 250 mg | 26-3 (12-2) | 5/52 (10) |
| single dose + TCS (n = 53) | | |
| Lebrikizumab 125 mg q4w + TCS (n = 51) | 26-9 (11-7) | 3/50 (6) |
| All lebrikizumab + TCS (n = 156) | n/a | 15/156 (10) |
| AD-1021 (dupilumab phase 2b)\textsuperscript{4} | | |
| Dupilumab 100 mg q4w (n = 65) | 32-2 (13-5) | 1/65 (2) |
| Dupilumab 300 mg q4w (n = 65) | 29-4 (11-5) | 4/65 (6) |
| Dupilumab 200 mg q2w (n = 61) | 32-9 (15-5) | 6/61 (10) |
| Dupilumab 300 mg q2w (n = 64) | 33-8 (14-5) | 3/64 (5) |
| Dupilumab 300 mg qw (n = 63) | 30-1 (11-2) | 7/63 (11) |
| All dupilumab (n = 318) | 31-7 (13-4) | 21/318 (7) |

EASI, Eczema Area and Severity Index; HLT, MedDRA high level term; MedDRA, Medical Dictionary for Regulatory Activities; n/a, not available; n1/N, number of patients with an event, per number of patients in the safety analysis set (comprising all patients who received ≥ 1 dose of study drug, by treatment received).\textsuperscript{4,5} TCS, topical corticosteroids; q2w, every 2 weeks; q4w, every 4 weeks; qw, weekly. MedDRA HLT of conjunctival infections, irritations and inflammation.\textsuperscript{5} Patients with ≥ 1 event.

References

1 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.
2 Waldman R, DeWane ME, Sloan SB. Does IL-4 inhibition play a role in dupilumab-associated conjunctivitis? Br J Dermatol 2020; 182:251.
3 Simpson EL, Flohr C, Eichenfield LF et al. Efficacy and safety of lebrikizumab (an anti-IL-13 monoclonal antibody) in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical corticosteroids: a randomized, placebo-controlled phase II trial (TREBLE). J Am Acad Dermatol 2018; 78:863–71.
4 Thaçi D, Simpson EL, Beck LA et al. Efficacy and safety of dupilumab in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical therapies: a randomised, placebo-controlled dose-ranging phase 2b study. Lancet 2016; 387:40–52.
5 Akinlade B, Guttman-Yassky E, de Bruin-Weller M et al. Conjunctivitis in dupilumab clinical trials. Br J Dermatol 2019; 181:459–73.
6 Treister AD, Kraff-Coope C, Lio PA. Risk factors for dupilumab-associated conjunctivitis in patients with atopic dermatitis. JAMA Dermatol 2018; 154:1208–11.
Dear Editor, The continuing increase in skin cancer incidence has not been curbed by campaigns raising people’s awareness of the risks of habitual excessive sun exposure. An approach to combat this which appears to be gaining momentum is to promote rigorous sunscreen use. The well-documented consensus review of Passeron et al. fits this approach and supports it by dismissing any adverse effect on vitamin D, their summary concluding: ‘Sunscreen use for daily and recreational photoprotection does not compromise vitamin D synthesis, even when applied under optimal conditions.’

Earlier reviews already found that sunscreen use (mainly for recreational sun protection) did not impair vitamin D status by summer-end. Residual shorter periods of unprotected sun exposure or inadequate sunscreen application were inferred to provide sufficient ultraviolet radiation (UVR) exposure. A recent systematic review also concluded there is little evidence that sunscreens decrease 25(OH)D concentration when used in real life; however, studies of rigorous use in low-UVR locations were absent. The pioneering work of Holick and group indicated that vitamin D production in sunlight plateaus at 1–5–3 minimal erythema doses (MEDs) in skin type III. Hence, acute overexposure by sunbathing is less effective for vitamin D synthesis than frequent lower-level exposure. Moreover, application during overexposure will not reduce vitamin D production in direct proportion to the sun protective factor (SPF), and in a high UVR environment the low-level daily exposure that enables sufficient vitamin D production can still be achieved, clearly in agreement with controlled SPF15 sunscreen use during a holiday in Tenerife.

Early reviews showed sunscreen use is inconsistently related to risk of melanoma or sunburn; confounding factors may operate. A more rigorous regimen of sunscreen use, in white people of European descent living under extreme ambient sun exposure in North-Eastern Australia, proved effective in protecting against squamous cell carcinoma, melanoma and photoageing. However, extrapolating effectiveness to discretionary sunscreen use in moderate climates (e.g. North-Western Europe) is questionable. A demand for rigorous daily sunscreen use is apparently favoured by Passeron et al., but their claim that this will not compromise vitamin D synthesis is unsubstantiated.

We concur with their statement: ‘It was estimated that the daily UVR dose through the sunscreen was 0–4 SED [standard erythemal dose], which is equivalent to 0–1 MED in a fair-skinned person. Thus, the UVB doses needed for the biosynthesis of vitamin D3 are indeed very low. Overall, this study shows that it is possible to have the benefits or solar exposure while minimizing the risks.’ Studies in volunteers in Manchester, UK have documented the relationship between both everyday sun exposure and vitamin D status, and the increase in 25(OH)D level to sufficiency under low-level simulated sun exposure. Based on these data, the required sun exposure for a white-skinned person to attain sufficient vitamin D equates to <4 SED weekly, or <1 SED daily, values below saturation in vitamin D production or risk of erythema. Thus, we are in good agreement with Passeron et al. about the regime for balancing the risk–benefit of UVR exposure. Where we take issue is with the call for global sunscreen use in everyday life; at middle–high latitudes this may result in vitamin D insufficiency in a substantially increased percentage of the population, and lengthen and deepen the ‘vitamin D winter low’.

High-quality studies examining the impact of rigorous sunscreen use on vitamin D status under routine daily-life conditions await performance at lower UVR locations. Meanwhile, a more nuanced public health message is indicated.

F.R. de Gruijl, A.R. Webb and L.E. Rhodes

Department of Dermatology, Leiden University Medical Center, 2333 ZA, Leiden, the Netherlands; 2Centre for Atmospheric Sciences, School of Earth and Environmental Sciences, University of Manchester, Manchester, UK; and 3Centre for Dermatology Research, School of Biological Sciences, Faculty of Biology, Medicine and Health, The University of Manchester and Salford Royal NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK

Correspondence: L.E. Rhodes.
E-mail: Lesley.e.rhodes@manchester.ac.uk

References
1 Passeron T, Bouillon R, Callender V et al. Sunscreen photoprotection and vitamin D status. Br J Dermatol 2019; 181: 916–31.
2 Neale RE, Khan SR, Lucas RM et al. The effect of sunscreen on vitamin D: a review. Br J Dermatol 2019; 181: 907–15.
3 Holick MF, MacLaughlin JA, Doppelt SH. Regulation of cutaneous previtamin D3 photosynthesis in man: skin pigment is not an essential regulator. Science 1981; 211: 590–2.
4 Young AR, Narbutt J, Harrison GI et al. Optimal sunscreen use, during a sun holiday with a very high ultraviolet index, allows vitamin D synthesis without sunburn. Br J Dermatol 2019; 181: 1052–62.
5 Webb AR, Kiff R, Durkun MT et al. The role of sunlight exposure in determining the vitamin D status of the U.K. white adult population. Br J Dermatol 2010; 163: 1050–5.