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%; $P < 0{\cdot}001$). Logistic regression analysis also showed that positive ANA [odds ratio (OR) 10·0; $p < 0{\cdot}0001$] was associated with prior-onset disease. Positive ANA (OR 16·3; $P < 0{\cdot}001$) and younger age at the time of CLE diagnosis [OR 1·04 (per 10 year decrease); $P = 0{\cdot}04$] 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 ($P = 0{\cdot}002$) (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.[1,2] 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.[1,2] In contrast, new-onset autoimmune conditions were predominantly SLE, at rates similar to those found in previous reports.[7,8] In spite of this, 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%).[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.

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

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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).[1] In response,

Waldman *et al.*[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.[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),[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,[5] but baseline severity was lower in TREBLE[3] than AD-1021 (see Table 1) or other dupilumab trials.[4,5]

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

	Baseline EASI (mean, SD)	Conjunctivitis,[a] n1/N (%)[b]
TREBLE (lebrikizumab phase 2)[3]		
Lebrikizumab 125 mg single dose + TCS (n = 52)	24·6 (11·1)	7/54 (13)
Lebrikizumab 250 mg single dose + TCS (n = 53)	26·3 (12·2)	5/52 (10)
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)[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);[3,4] TCS, topical corticosteroids; q2w, every 2 weeks; q4w, every 4 weeks; qw, weekly. [a]MedDRA HLT of conjunctival infections, irritations and inflammation. [b]Patients with ≥ 1 event.

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;[6] however, in TREBLE, treatment was for ≤ 12 weeks,[3] likely underestimating IL-13 blockade effects.

Conjunctivitis seen in dupilumab AD trials is a complex, multifactorial phenomenon.[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,[5] and conjunctivitis was not an issue in asthma trials of dupilumab (very low rates, similar for dupilumab and placebo).[5] Conjunctivitis usually resolves while patients are on dupilumab and is rarely treatment limiting,[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.

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Everyday sunscreen use may compromise vitamin D in temperate climes

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Linked Article: Passeron *et al. Br J Dermatol* 2019; 181: 916–31.

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.*[1] 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;[2] however, studies of rigorous use in low-UVR locations were absent. The pioneering work of Holick and group[3] 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.[4]

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.*,[1] 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.'[1] Studies in volunteers in Manchester, UK have documented the relationship between both everyday sun exposure and vitamin D status,[5] and the increase in 25(OH)D level to sufficiency under low-level simulated sun exposure.[6] 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,[7] values below saturation in vitamin D production or risk of erythema. Thus, we are in good agreement with Passeron *et al.*[1] 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.

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