Table 1 Cumulative incidence proportions and standardized incidence ratios of specific cancers among patients with psoriasis with venous thromboembolism (VTE), Denmark, 1996–2018

Time and cancer site	Cumulative incidence proportion (95% CI)	O/E[a]	Standardized incidence ratio (95% CI)
0–1 year after VTE diagnosis			
All	4·7 (3·5–6·3)	42/13·9	3·0 (2·2–4·1)
Lung, bronchi and trachea	1·0 (0·5–1·9)	9/1·4	6·4 (3·0–12·3)
Basal cell skin cancer	0·6 (0·2–1·3)	5/3·1	1·6 (0·5–3·8)
> 1 year after VTE diagnosis			
All	27·1 (20·2–34·5)	103/70·2	1·5 (1·2–1·8)
Colorectal	1·9 (0·9–3·7)	8/7·3	1·1 (0·5–2·2)
Lung, bronchi and trachea	2·8 (1·5–4·7)	13/6·7	1·9 (1·0–3·3)
Other skin cancer (excluding basal cell skin cancer)	1·4 (0·5–3·2)	5/3·4	1·5 (0·5–3·4)
Breast cancer	3·9 (0·6–12·4)	7/6·7	1·1 (0·4–2·2)
Non-Hodgkin malignant lymphoma	3·4 (1·3–7·0)	8/2·3	3·4 (1·5–6·8)
Basal cell skin cancer	7·3 (4·9–10·3)	31/16·2	1·9 (1·3–2·7)

CI, confidence interval. [a]Observed cancer incidence compared with the expected based on national cancer statistics. Only cancer sites with five or more events are presented, to ensure anonymity, as required by Danish legislation.

The pathogenetic mechanisms of thrombosis in cancer involve a complex interaction between tumour cells, activation of blood coagulation such as in acute-phase reactions, paraprotein production, inflammation, necrosis and haemodynamic disorders. Malignant cells can activate blood coagulation by releasing proinflammatory and proangiogenic cytokines and by interacting with vascular and blood cells.[4]

It has been thought that patients with idiopathic or primary VTE are at higher risk of occult cancer than patients with a venous thrombotic event secondary to a provoking factor.[5] However, several studies have shown that VTE in patients with chronic diseases like psoriasis may also be a marker for occult cancer.[6]

Comprehensive research has shown that extensive screening for occult cancer in patients with VTE in general will lead to a higher rate of cancer detection, but these strategies have not been associated with improved cancer-related mortality.[7] It is not clear from existing literature whether some subgroups of patients, like those with psoriasis, may benefit from extensive diagnostic investigations for cancer. Therefore, patients with psoriasis with a VTE should follow the same guidelines for occult cancer screening as other patients with VTE, until more evidence becomes available.[8]

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Dupilumab-associated head and neck dermatitis is associated with elevated pretreatment serum *Malassezia*-specific IgE: a multicentre, prospective cohort study

DOI: 10.1111/bjd.21019

Dear Editor, Dupilumab-associated head and neck dermatitis (DAHND) refers to the *de novo* development or exacerbation of

head and neck dermatitis (HND) in the setting of dupilumab therapy.[1,2] It has been observed in 10% of atopic patients,[3,4] with the causative mechanisms incompletely understood. Proposed hypotheses have included site-specific treatment failure of dupilumab as well as localized inflammatory reaction to facial *Malassezia* species.[5,6,7]

This prospective cohort study aimed to assess whether baseline (pretreatment) *Malassezia*-specific IgE levels were associated with the development of DAHND in individuals commencing dupilumab therapy for moderate-to-severe atopic dermatitis. Over a 6-month period from 1 March 2021 to 1 September 2021, 171 consecutive patients were included.

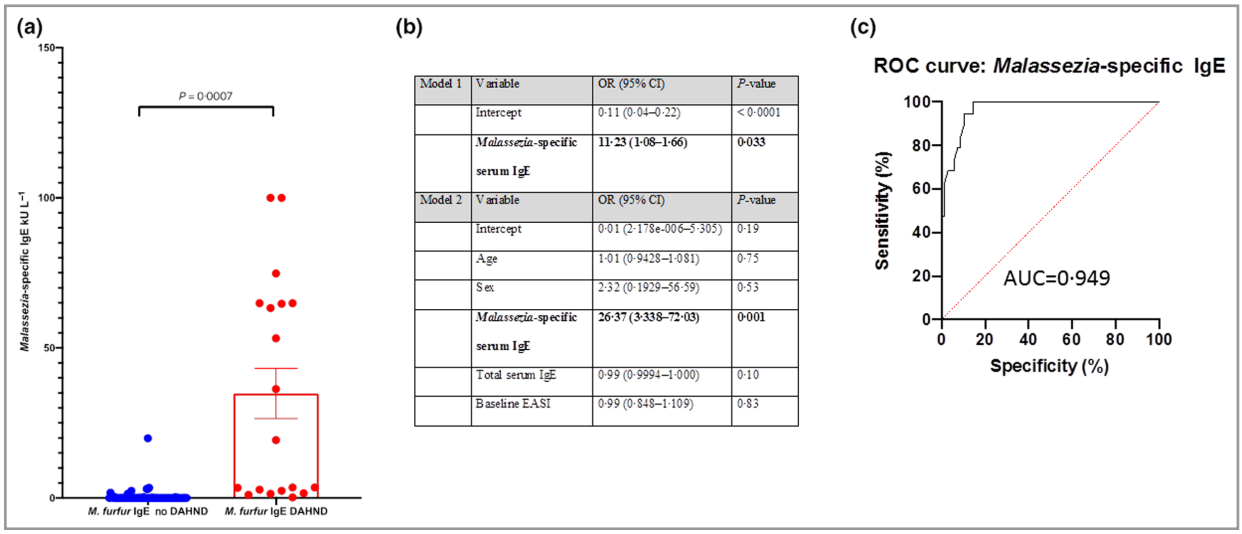
Age, sex, Eczema Area and Severity Index (EASI) score, total serum IgE and *Malassezia*-specific serum IgE as measured by ImmunoCAP solid phase sandwich immunoassay (Thermo Fisher Scientific, Waltham, MA, USA) were recorded. DAHND was defined as *de novo* or worsening (defined as a 50% worsening in head and neck EASI score)[5] HND after dupilumab commencement.

Statistical analysis was conducted using Prism 8.4.2 (GraphPad Software, Inc., San Diego, CA, USA). Univariate analysis was undertaken to examine the relationships between DAHND and a priori variables including age, sex, baseline EASI, baseline head and neck EASI subscore, baseline total IgE, baseline *Malassezia*-specific IgE, and ratios of *Malassezia*-IgE to total IgE. Gaussian distribution was not assumed, and nonparametric tests were utilized. Chi-squared tests were used for binary variables (sex), and Wilcoxon rank-sum tests for continuous variables. Significance was defined at $P < 0{\cdot}05$, and adjustment for multiple comparisons made using Bonferroni correction. Logistic regression analysis was performed to assess the relationship between DAHND and baseline *Malassezia*-specific IgE. A second logistic regression model was developed assessing the relationship between DAHND and baseline *Malassezia*-specific IgE and the a priori identified covariates. Receiver operating curves (ROCs) were produced for total serum IgE, total serum *Malassezia*-specific IgE and *Malassezia* IgE: total IgE ratio; and sensitivity and specificity were calculated.

Of the 171 consecutive participants included, 25 (14·7%) were diagnosed with DAHND. All patients with DAHND demonstrated EASI 75 (75% reduction from baseline in EASI response). Comparing individuals with DAHND and without DAHND, no statistically significant differences were identified between sex ($P = 0{\cdot}31$), age (median 31 years vs. 35 years; $P = 0{\cdot}23$), baseline EASI score (35·7 vs. 36·1; $P = 0{\cdot}88$) or severity of baseline head and neck dermatitis (EASI 0·1 vs. 0·2; $P = 0{\cdot}95$).

There was a statistically significant difference in serum *Malassezia*-specific IgE between DAHND and non-DAHND groups (median 31·95 kU L^{-1} vs. 2·27 kU L^{-1}; $P = 0{\cdot}005$) (Figure 1a). No statistically significant difference was seen in baseline serum total IgE levels (4570 kU L^{-1} vs. 4478 kU L^{-1}; $P = 0{\cdot}95$). Unadjusted logistic regression analysis (Figure 1b) identified increased odds of DAHND with every 1 kU mL^{-1} increase in baseline serum *Malassezia*-specific IgE [odds ratio (OR) 11·23, 95% confidence interval (CI) 3·68–63·73]. When adjusted for covariates (Figure 1b), there were greater odds of DAHND with every 1 kU mL^{-1} increase in baseline serum *Malassezia*-specific IgE (OR 26·37, 95% CI 4·98–952·7). No examined covariates (age, sex, baseline EASI and total serum IgE) were statistically significant in altering the odds of DAHND.

ROC demonstrated a greater area under the curve (AUC) when examining the logistic regression model (AUC = 0·984) and *Malassezia*-specific serum IgE model (AUC = 0·949) (Figure 1c) compared with total IgE (AUC = 0·643). Using the previously reported cut-off for determination of a positive



Model 1	Variable	OR (95% CI)	*P*-value
	Intercept	0·11 (0·04–0·22)	< 0·0001
	***Malassezia*-specific serum IgE**	**11·23 (1·08–1·66)**	**0·033**
Model 2	**Variable**	**OR (95% CI)**	***P*-value**
	Intercept	0·01 (2·178e-006–5·305)	0·19
	Age	1·01 (0·9428–1·081)	0·75
	Sex	2·32 (0·1929–56·59)	0·53
	***Malassezia*-specific serum IgE**	**26·37 (3·338–72·03)**	**0·001**
	Total serum IgE	0·99 (0·9994–1·000)	0·10
	Baseline EASI	0·99 (0·848–1·109)	0·83

Figure 1 (a) Comparison of levels of *Malassezia*-specific serum IgE, stratified by the presence of dupilumab-associated head and neck dermatitis (DAHND) or no DAHND. (b)Logistic regression analysis of factors associated with DAHND not including (model 1) and including (model 2) a priori covariates. (c) Receiver operating characteristic (ROC) curve and area under the curve (AUC) analysis of *Malassezia*-specific serum IgE. OR, odds ratio; CI, confidence interval; EASI, Eczema Area and Severity Index. Variables and their P-values shown in bold were considered statistically significant ($P < 0{\cdot}05$).

result for *Malassezia*-specific IgE (0·35 kU mL^{-1}), a positive baseline serum *Malassezia*-specific IgE demonstrated a 94·1% sensitivity and 87·9% specificity for diagnosis of DAHND.

All participants experiencing DAHND were treated at the physician's discretion, as no treatment standard for DAHND exists. Two of the 25 (8%) had topical mild-to-moderate corticosteroid or topical calcineurin inhibitor monotherapy prescribed, with a 100% (two of two) response rate. Thirteen of the 25 (52%) had combination corticosteroid/antifungal therapy (ketoconazole or clotrimazole) prescribed, with an 85% (11 of 13) response rate. Ten of 25 (40%) received itraconazole 200 mg twice daily for up to 28 days, with a 70% (seven of 10) response rate. Twenty of 25 (80%) experienced DAHND recurrence after cessation of therapy, and three of 25 (12%) discontinued dupilumab due to DAHND after failed itraconazole therapy.

The prospective nature of this study brings credence to the concept that *Malassezia*-specific serum IgE may represent a potential safety biomarker in the setting of treatment of atopic dermatitis with dupilumab. This is supported by the high level of sensitivity and specificity identified in ROC analysis. Unfortunately, improvement in DAHND with therapy was often transient. This study is limited by short-term follow-up (28 weeks).

The potential mechanisms of DAHND can be postulated to involve prior *Malassezia*-specific IgE sensitization, based on the results of this study and the observation of other authors.[3–7] The mechanism of action of dupilumab suggests that the mechanism of DAHND is likely to be independent of the Th2-mediated pathways suppressed by dupilumab therapy.[8] In conclusion, baseline *Malassezia*-specific IgE may be used as a biomarker to predict DAHND prior to dupilumab therapy.

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Data availability: the data that support the findings of this study are available from the corresponding author on reasonable request.

The incidence of chronic itch in patients on haemodialysis and associated factors

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Dear Editor, Chronic itch (CI) is a frequent symptom in many skin diseases and also occurs in a number of systemic diseases, such as chronic kidney disease. CI is very bothersome for patients on haemodialysis (HD) in particular, and this symptom is still not well understood and can be difficult to treat.[1,2] Today there are few treatment options, and these have a moderate effect on CI in patients on HD.[3] However, difelikefalin, a selective κ-opioid receptor agonist, was positively evaluated in a recent placebo-controlled phase III trial for the treatment of CI in patients on HD.[4] A previous study that investigated patients in 12 Western countries has reported that up to 45% of all patients on HD were bothered by itch, at least to a moderate degree.[5] The German Epidemiological Hemodialysis Study (GEHIS) was initiated in 2013 in order to assess the prevalence