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**Title:** Comparison of real-world treatment outcomes of systemic immunomodulating therapy in atopic dermatitis patients with dark and light skin types

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A.L. Bosma, S.J. Brown, P.I. Spuls, C. Flohr and M.A. Middelkamp-Hup are investigators on the European Union Horizon 2020-funded BIOMAP Consortium (http://www.biomap-imi.eu/).

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P.I. Spuls has done consultancies in the past for Sanofi 111017 and AbbVie 041217 (unpaid), received a departmental independent research grants for TREAT NL registry from Pharma since December 2019, is involved in performing clinical trials with many pharmaceutical industries that manufacture drugs used for the treatment of e.g. psoriasis and atopic dermatitis, for which financial compensation is paid to the department/hospital and, is Chief Investigator (CI) of the systemic and phototherapy atopic eczema registry (TREAT NL) for adults and children.

C. Flohr is Chief Investigator of the UK National Institute for Health Research-funded TREAT (ISRCTN15837754) and SOFTER (Clinicaltrials.gov: NCT03270566) trials as well as the UK-Irish Atopic eczema Systemic Therapy Register (A-STAR; ISRCTN11210918) and a Principle Investigator in the European Union (EU) Horizon 2020-funded BIOMAP Consortium (http://www.biomap-imi.eu/). He also leads the EU Trans-Foods consortium. His department has received funding from Sanofi-Genzyme for skin microbiome work.

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**Abbreviations and acronyms:** AD: atopic dermatitis; AE: adverse event; DLQI: Dermatology Life Quality Index; DST, Dark Skin Type(s); EASI: Eczema Area and Severity Index; IQR: interquartile range; LST, Light Skin Type(s); NRS: Numerical Rating Scale; POEM: Patient-Oriented Eczema Measure; SD: Standard Deviation.

**Abstract**

*Background:* Few data exist on differences in treatment effectiveness and safety in atopic dermatitis patients of different skin types.

*Objective:* To investigate treatment outcomes of dupilumab, methotrexate, and ciclosporin, and morphological phenotypes in atopic dermatitis patients, stratified by Fitzpatrick skin type.

*Methods:* In an observational prospective cohort study, pooling data from the Dutch TREAT NL and UK-Irish A-STAR registries, data on morphological phenotypes and treatment outcomes were investigated.

*Results:* 235 patients were included (light skin types (LST): Fitzpatrick skin type 1-3: n=156 (Ethnicity: White: 94.2%), dark skin types (DST): skin type 4-6: n=68 (Black African/Afro-Caribbean: 25%, South-Asian: 26.5%, Hispanics: 0%)). DST were younger (19.5 vs. 29.0 years;p<0.001), more often had follicular eczema (22.1% vs. 2.6%;p<0.001), higher baseline EASI scores (20.1 vs. 14.9;p=0.009), less allergic contact dermatitis (30.9% vs. 47.4%;p=0.03) and less previous phototherapy use (39.7% vs. 59.0%;p=0.008). When comparing DST and LST corrected for covariates including baseline EASI, DST showed greater mean EASI reduction between baseline and 6 months with only dupilumab (16.7 vs. 9.7; adjusted p=0.032). No differences were found for adverse events for any treatments (p>0.05).

*Limitations:* Unblinded, non-randomized.

*Conclusion:* Atopic dermatitis differs in several characteristics between LST and DST. Skin type may influence treatment effectiveness of dupilumab.

**Introduction**

Atopic dermatitis (AD), also known as atopic eczema, is a chronic pruritic inflammatory skin disorder which is among the most common dermatological conditions. AD is more prevalent in black and mixed race populations and differences seem to exist between AD in darkly pigmented and light skin, including variations in genetics and immunology.1-6 Dark skin has been shown to have inherent structural properties that may trigger pruritus, such as higher transepidermal water loss and an increased size of mast cells.7, 8 Higher natural moisturizing factor levels and down-regulated keratinocyte differentiation have been shown in dark skin compared to light skin, suggesting differences in pathophysiological mechanisms.9-11 This may imply a potential biological basis for differences in treatment response between light and dark skin. Clinically, AD can also present differently in dark skin.4, 5, 6 Follicular eczema is an example of a morphological phenotype that is more frequently seen in African-American, Hispanic, and Asian patients.12 A systematic review confirmed differences in morphological AD characteristics by study region.13 Nevertheless, studies investigating the effectiveness and safety of systemic therapy in AD patients of different skin types are lacking, and only a few studies focus on this topic.14-20 Studies investigating treatments in AD patients are predominantly conducted in white patients.14

In this study we aimed to investigate the effectiveness and safety of dupilumab, ciclosporin and methotrexate in AD patients with different skin types. In addition, we wanted to investigate the association between morphological phenotypes and skin types. We hypothesized that AD patients with dark skin types (DST) have different treatment outcomes and morphological phenotypes compared to patients with light skin types (LST). We specifically focused on skin type instead of ethnicity or race, as skin type could be determined more objectively. Ethnicity or race are complex terminologies that, in addition to skin colour may also cover country of origin, physical features, cultural traditions and the concept of mixed ethnicity. We hypothesized skin type to be a proxy for genetic differences between patients, underlying potential differences in pathophysiology, and subsequently, morphology and treatment response.

**Methods**

*Study design*

We conducted a registry-embedded observational prospective cohort study, using real-world data from the Dutch TREAT (TREatment of ATopic eczema) NL (treatregister.nl) and UK-Irish A-STAR (Atopic eczema Systemic TherApy Register; astar-register.org) registries.

*Setting*

Patients were included at two centers in the Netherlands (November 2017 to June 2020), and 13 centers in the United Kingdom (October 2018 to April 2021). Study visits were at baseline, 4 weeks, and then approximately every 3 months, alongside routine clinic appointments.

*Participants*

Eligible patients were all children and adults with AD according to the U.K. working party’s diagnostic criteria, starting treatment with dupilumab, ciclosporin and/or methotrexate in the context of routine clinical care. All dupilumab patients met the national criteria for dupilumab treatment, which stipulate prior treatment of at least 4 months with 1 or more conventional systemic therapies. Patients were allowed to use other systemic immunomodulating treatments and topical treatments concomitantly. The study size resulted from the inclusion of eligible patients in the abovementioned timeframes.

*Variables*

Data collection was based on the TREAT Registry Taskforce core dataset.21, 22 Data on Fitzpatrick skin type and morphological phenotype based on standardized proforma (e.g. (non-)flexural eczema, palmar hyperlinearity, pompholyx, discoid eczema, nodular prurigo, follicular eczema, keratosis pilaris, erythroderma, ichthyosis vulgaris; definitions included in supplementary material 1) were collected. LST were defined as Fitzpatrick skin types 1-3, and DST as Fitzpatrick skin types 4-6. Effectiveness was analyzed using the Eczema Area and Severity Index (EASI),23 Numerical Rating Scale (NRS) peak pruritus past 24 hours,24 Patient-Oriented Eczema Measure (POEM)25 and Dermatology Life Quality Index (DLQI), Children's DLQI (CDLQI) or Infants' Dermatitis Quality of Life Index (IDQLI).26 Safety was assessed through the reporting of adverse events at each visit (AEs; definitions are included in Supplementary table 1a).

*Definition of treatment endpoint*

In previous studies, comparison of the effectiveness of methotrexate and ciclosporin at the same predefined treatment endpoint was considered a disadvantage due to differences in speed of action.27, 28 Therefore, we defined appropriate treatment endpoints per treatment . Methotrexate has a relatively slow onset of action, and we therefore chose 6 months as treatment endpoint. To allow direct comparisons, we chose the same endpoint for dupilumab, even though the drug has a faster onset of action. In our dataset, ciclosporin was often terminated before 6 months of treatment, for instance because of side effects or ineffectiveness. As ciclosporin has a fast onset of action, we therefore analyzed the data at 3 months instead.

*Statistical analyses*

Patient characteristics, safety and treatment discontinuation data were summarized using descriptive statistics and assessed during the entire follow-up period of this study. For univariate comparisons, Mann-Whitney tests and chi-squared tests were used as appropriate.

Baseline scores were compared to treatment endpoint scores using paired t-tests. To investigate differences between treatment groups in delta scores and the course of scores over time, we used linear mixed-effects models with an interaction between time and treatment. Natural Cubic Splines were used to model the scores over time, with the optimal degrees of freedom based on the minimal Bayesian Information Criterion. To test if there is a difference between skin types in scores during treatment, an ANOVA test was conducted to assess the difference between the model with skin type and a model where this interaction term was removed. We included a random intercept for each patient and, in addition to skin type, included variables for which we found a significant difference between DST and LST in the models as potential confounders (including age, baseline severity score, follicular eczema, allergic contact dermatitis and previous phototherapy use). Missing values for the covariates were included as unknown.

Effects were considered statistically significant if p<0.05. Analyses were performed using SPSS 24.0 (IBM, Armonk, NY, U.S.A.) and R version 3.4.1 (Foundation For Statistical Computing, Vienna, Austria).

We have included a RECORD/STROBE checklist as supplementary material 2.

**Results**

*Baseline patient characteristics*

In total, 235 patients were included (Table 1). The majority of patients were male (59.1%), 67.7% were white, 156 patients (66.4%) had LST and 68 patients (28.9%) DST. Skin types of 11 patients were missing and excluded from analyses comparing skin types.

DST were on average younger when entering the registries compared to LST (median age 19.5 vs. 29.0 years; p<0.001). Higher baseline EASI scores were recorded in DST (20.1 vs. 14.9; p=0.009). Allergic contact dermatitis and previous use of phototherapy were more prevalent in LST (47.4% vs. 30.9%; p=0.026 and 59.0% vs. 39.7%; p=0.008, respectively). We also found a correlation between ethnicity and skin type (p<0.001).

*Effectiveness according to skin type*

In total, 168 patients were treated with dupilumab (LST: n=121 (72.0%), DST: n=42 (25.0%)), 65 patients with methotrexate (LST: n=37 (56.9%), DST: n=22 (33.8%)) and 26 patients with ciclosporin (LST: n=19 (73.1%), DST: n=7 (26.9%)).

For dupilumab and methotrexate, an ANOVA test revealed a significant p-value for skin type as interaction term for EASI (p<0.001 and p=0.04, respectively), indicating that the course of EASI over time differs between DST and LST. Results of the linear mixed-effects models displaying the course of the scores over time according to skin type are shown for EASI only (Figure 1). Both skin type groups show improvement over time. Other scores are shown in Supplementary figure 1-3.

To get insight into how DST and LST are different, we compared baseline scores to treatment endpoint scores (Table 2). Significant improvement over time was observed for all outcome measures in both skin type groups when treated with dupilumab (i.a. ΔEASI for DST: 16.7; p<0.001, ΔEASI for LST: 9.7; p<0.001). LST also showed significant improvement in all outcome measures for methotrexate (i.a. ΔEASI: 11.0; p=0.019) and ciclosporin (i.a. ΔEASI: 13.1; p<0.001). In DST treated with methotrexate and ciclosporin, EASI showed significant improvement for methotrexate (Δ5.7; p=0.048) and borderline significant improvements were found for DLQI (Δ4.9; p=0.051) for methotrexate and EASI for ciclosporin (Δ12.9; p=0.054). Both groups reached the minimal clinically important difference (MCID)29-31 for all outcomes with dupilumab. For methotrexate, patients with DST did not reach the MCID for EASI, POEM and NRS pruritus. For ciclosporin, DST did not reach the MCID for NRS pruritus. When comparing DST and LST, DST showed a significantly greater improvement in EASI when treated with dupilumab, even after adjustment for age, baseline severity, follicular eczema, allergic contact dermatitis and previous phototherapy use (Δ16.7 vs. Δ9.7;p=0.032; Table 2). We found no difference in EASI improvement between DST and LST for methotrexate and ciclosporin, as well as no difference in any of the other scores for all treatments.

*Concomitant therapy during follow-up*

In total, 31 (18%), 13 (20%) and 7 (27%) patients used conventional systemic therapy concomitantly with dupilumab, methotrexate and ciclosporin, respectively (Supplementary table 2a-c). No differences were found for usage of concomitant systemic therapy or mean usage duration between DST and LST (p>0.05).

*Safety*

In total, 79 potentially related adverse events were reported during the study (Supplementary table 1a-c). No serious adverse events were reported. In none of the treatment groups differences were found in the total number of adverse events, when comparing DST and LST (p>0.05).

*Treatment discontinuation*

A significant difference in treatment discontinuation was found between treatments, with most discontinuation for ciclosporin (n=12/26, 46.2%), followed by methotrexate (n=20/65, 30.8%) and dupilumab (n=23/168, 13.7%) (p<0.001). The most frequent reasons for discontinuation were side-effects and/or treatment ineffectiveness (Supplementary table 3). However, no differences in treatment discontinuation were found between DST and LST (p>0.05).

*Differences in morphological phenotypes*

We found a higher prevalence of follicular eczema in DST (22.1% vs. 2.6%; p<0.001) (Table 1). No differences were found between skin types for the other morphological features ((non-)flexural eczema, palmar hyperlinearity, pompholyx, discoid eczema, nodular prurigo, keratosis pilaris, erythroderma, ichthyosis vulgaris, infraorbital Dennie-Morgan skin folds and infra-auricular fissure(s)). No analyses could be performed to investigate if the morphological phenotypes respond differently to treatment due to low numbers.

**Discussion**

In this study we investigated treatment outcomes and morphological phenotypes in AD patients with DST vs. LST receiving treatment with dupilumab, methotrexate and ciclosporin in a daily practice setting. Patients with DST had significantly more severe disease at baseline, indicated by higher EASI. We found that EASI scores improved in both DST and LST when treated with dupilumab, methotrexate and ciclosporin, although this change did not reach statistical significance in DST ciclosporin patients, probably related to the small sample size. When comparing treatment effectiveness between DST and LST, DST patients showed a significantly greater EASI improvement in comparison to LST when treated with dupilumab after correction for baseline differences, but not with methotrexate or ciclosporin. No differences were found between DST and LST for total number of adverse events. Taken together, skin type may potentially influence treatment effectiveness of dupilumab, but does not seem to affect safety. Concerning morphological phenotypes, follicular eczema was significantly more common in DST.

DST patients had significantly higher baseline EASI scores, indicating more severe disease at the time of inclusion. DST were also significantly younger. Higher disease severity in DST has been reported previously,1-4 and a retrospective study showed that children with treatment resistant AD more often had DST.32 Patients with skin type IV were also found to have higher scores of EASI, DLQI and Investigator Global Assessment, compared to patients with Fitzpatrick skin type II.33 Nonetheless, our registries contain more patients with LST than DST. This may result from the geographical location of the including centers, or it may reflect a potential disparity in receiving systemic therapies amongst the subgroups. Other studies showed racial and ethnic disparities in receiving therapies in AD and other diseases.34, 35 Black psoriasis patients are reported to be less likely to receive biologics than white patients due to potential financial and racial barriers in the US.36 More research on disparities in receiving systemic AD therapies and potential causal factors of differences in severity amongst subgroups would be of interest. 37-39

We found that allergic contact dermatitis was more prevalent in LST vs. DST. Dark skin has been shown to be less permeable compared to light skin,40, 41 and this could be a possible explanation. Another explanation could be that allergic contact dermatitis is more difficult to diagnose in DST. However, it may also be possible that LST are more commonly investigated for contact allergy, e.g. because they have better access to healthcare. The higher numbers of previous phototherapy in LST could be explained by a higher age in this subgroup. No statistically significant differences were found between DST vs. LST for other characteristics, such as age of onset, BMI, educational status, family AD history and allergic diseases and concomitant therapy use.

Regarding morphology, we found significantly more follicular eczema in DST. Others have described follicular eczema in Hispanic and Asian populations,12,42-44 rather than directly comparing populations or focusing on skin type as was done in this study. Follicular eczema is characterized by follicular prominence clinically and follicular spongiosis histopathologically.12 Remarkably, the investigated morphological characteristics (e.g. pompholyx, discoid eczema, nodular prurigo, keratosis pilaris, erythroderma and ichthyosis vulgaris) were only present in a small minority of patients. Due to limited numbers, we were not able to investigate treatment effects within morphological phenotypes.

In our registries, dupilumab was most frequently prescribed (71%), followed by methotrexate (28%) and ciclosporin (11%). Interestingly, prescription of methotrexate was more common than ciclosporin, despite the latter being an on-label treatment option for adults. For all treatments, side-effects were the main reason for discontinuation of treatment, followed by ineffectiveness.

Several limitations result from the daily practice setting. Due to the absence of randomization for treatment allocation, differences may arise in treatment groups because of selection bias. Dupilumab treatment requires previous use of conventional systemics. Also, bias may have been induced by the non-blinded observational nature of the study, including for severity assessments, with erythema being particularly difficult to assess in DST. We also had relatively low numbers of DST, especially in the methotrexate and ciclosporin groups. We did not stratify patients based on treatment dosage and included patients on combined systemic therapies. Only severe AEs were registered in the Netherlands as part of the TREAT core dataset.22

In summary, we found significant differences between AD patients with DST and LST, such as more severe disease at baseline and more follicular eczema in DST. Importantly, skin type may also influence treatment effectiveness of dupilumab in AD, as DST showed significantly greater EASI improvement than LST. Larger studies are needed to confirm these results, and skin type should therefore be considered a confounder in future AD intervention studies. Moreover, further research investigating whether morphological phenotypes respond differently to treatments is needed.

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**Figure legends**

**Figure 1. Difference in Eczema Area and Severity Index (EASI) from baseline (delta EASI) over time for each treatment group**

Estimated mean differences in EASI scores from baseline (including 95% confidence interval) for our linear mixed-effects models, with continuous values for time and time displayed in weeks and corrected for age, baseline EASI scores, follicular eczema, allergic contact dermatitis and previous use of phototherapy, in patients with atopic dermatitis. Higher delta scores indicate greater improvement of disease activity and/or burden. The median follow-up duration for the outcome measurements varied from 38 to 46 weeks (IQR: 14-74 weeks) for dupilumab, from 17 to 19 weeks (IQR: 1-47 weeks) for methotrexate and from 15 to 17 weeks (IQR: 0-32 weeks) for ciclosporin. Dupilumab: n=168 at baseline (light skin types (LST): n=121; dark skin types (DST): n=42), n=125 at 6 months (LST: n=90; DST: n=35). Methotrexate: n=65 at baseline (LST: n=37; DST: n=22), n=25 at 6 months (LST: n=15; DST: n=10). Ciclosporin: n=26 at baseline (LST: n=19; DST: n=7), n=15 at 3 months (LST: n=11; DST: n=4).

**Tables**

**Table 1. Baseline patient characteristics**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Study cohort(n=235)a | Light skin type(n=156, 66.4%) | Dark skin type(n=68, 28.9%) | p-value |
| Sex – no. (%): Male/Female | 139 (59.1)/96 (40.9) | 93 (59.6)/63 (40.4) | 40 (58.8)/28 (41.2) | 0.91 |
| Age, median (IQR) – years | 26.0 (14.0-45.0) | 29.0 (17.3-48.0) | 19.5 (13.0-32.3) | **<0.001** |
| Age of onset AD, median (IQR) – years1 | 0 (0-3) | 0 (0-3) | 0 (0-4) | 0.92 |
| EASI, median (IQR)2 | 17.0 (9.175-27.325) | 14.9 (7.6-25.8) | 20.1 (10.8-30.6) | **0.009** |
| NRS pruritus past 24h, median (IQR)3 | 7 (6-8) | 7 (6-8) | 7 (4-9) | 0.38 |
| POEM, median (IQR)4 | 21 (16-24) | 21 (16-24) | 20 (13-24) | 0.67 |
| DLQI, mean ± SD5 | 14.1 ± 7.0 | 13.8 ± 6.9 | 14.8 ± 7.2 | 0.32 |
| Patients per treatment group – no. (%)DupilumabMethotrexateCiclosporin | 168 (71.5)65 (27.7)26 (11.1) | 121 (77.6)37 (23.7)19 (12.2) | 42 (61.8)22 (32.4)7 (10.3) |  |
| BMI – median (IQR)b | 24.7 (22.6-27.8) | 24.7 (22.6-27.3) | 24.8 (21.8-30.1) | 0.63 |
| Educational statusc, 6ISCED 0-2: Early childhood, primary and lower secondary educationISCED 3-5: Upper secondary to short cycle tertiary educationISCED 6-8: Bachelor’s, Master’s, Doctoral or equivalent level | 57 (24.3)103 (43.8)64 (27.2) | 38 (24.4)73 (46.8)40 (25.6) | 14 (20.6)27 (39.7)21 (30.8) | 0.28 |
| Ethnicity – no. (%)7White (Europe, Russia, Middle East, North Africa, USA, Canada, Australia)Black African, Afro-CaribbeanAsian-ChineseSouth-Asian (India, Pakistan, Sri Lanka, Nepal, Bhutan, Bangladesh)Asian-other (Korea, China north of Huai River)Hispanic or LatinoMixedOther | 159 (67.7)18 (7.7)5 (2.1)23 (9.8)8 (3.4)1 (0.4)19 (8.1)1 (0.4) | 147 (94.2)0 (0)0 (0)4 (2.6)0 (0)1 (0.6)4 (2.6)d0 (0) | 4 (5.9)17 (25.0)5 (7.4)18 (26.5)7 (10.3)0 (0)15 (22.0)e1 (1.5) | **<0.001** |
| Fitzpatrick skin type – no. (%)6I/IIIII/IVV/VI | 17 (7.2)/87 (37.0)52 (22.1)/29 (12.3)29 (12.3)/10 (4.3) | 17 (10.9)/87 (55.8)52 (33.3)/0 (0)0 (0)/0 (0) | 0 (0)/0 (0)0 (0)/29 (42.6)29 (42.6)/10 (14.7) | **<0.001** |
| Fitzpatrick skin type – median (IQR) | 3 (2-4) | 2 (2-3) | 5 (4-5) | **<0.001** |
| Morphological phenotypes – no. (%)Flexural eczema8Non-flexural eczema8Palmar hyperlinearity9Pompholyx10Discoïd (syn. nummular) eczema11Prurigo nodularis12Follicular eczema13Keratosis pilaris14Erythroderma15Ichthyosis vulgaris16Infraorbital Dennie-Morgan skin folds17Infra-auricular fissure(s)18 | 169 (71.9)173 (73.6)64 (27.2)13 (5.5)7 (3.0)14 (6.0)19 (8.0)12 (5.1)14 (6.0)11 (4.7)13 (9.8)14 (10.5) | 113 (72.4)116 (74.4)45 (28.8)10 (6.4)4 (2.6)6 (3.8)4 (2.6)5 (3.2)9 (5.8)6 (3.8)10 (10.5)11 (11.6) | 49 (72.0)51 (75.0)18 (26.5)3 (4.4)3 (4.4)7 (10.3)15 (22.1)7 (10.3)3 (4.4)5 (7.4)3 (7.9)3 (7.9) | 0.960.310.290.840.410.13**<0.001**0.090.580.340.530.29 |
| Skin infection19 | 17 (7.2) | 11 (7.1) | 4 (5.9) | 0.95 |
| Allergic co-morbidities – no. (%)Asthmaf,7Allergic rhinoconjunctivitisf,7Atopic eye diseasef,20Eosinophilic oesophagitisf,20Allergic contact dermatitisgFood allergy | 128 (54.5)129 (54.9)18 (7.7)2 (0.8)97 (41.3)118 (50.2)h / 93 (39.6)i | 87 (55.8)92 (59.0)13 (8.3)1 (0.6)74 (47.4)76 (48.7)h / 63 (40.4)i | 41 (60.3)37 (54.4)5 (7.4)1 (1.5)21 (30.9)42 (61.8)h / 30 (44.1)i | 0.680.690.530.86**0.026**0.18 / 0.14 |
| Family history of AD and allergic diseasesj,21- no. (%) | 140 (59.6) | 98 (62.8) | 42 (61.8) | 0.84 |
| Previous use of systemic therapies for AD – no. (%)5CiclosporinAzathioprineMethotrexateMycophenolic acid/mycophenolate mofetilSystemic corticosteroidsDupilumabkOther medicationlInvestigational medication | 190 (80.9)127 (54.0)38 (16.2)96 (40.9)30 (12.8)99 (42.1)2 (0.9)2 (0.9)14 (6.0) | 134 (85.9)89 (57.1)29 (18.6)64 (41.0)19 (12.2)76 (48.7)0 (0)2 (1.3)11 (7.1) | 50 (73.5)35 (51.5)6 (8.8)28 (41.2)10 (4.7)23 (33.8)1 (1.5)0 (0)3 (4.4) | 0.0520.570.140.800.710.090.260.520.60 |
| Previous use of phototherapy – no. (%) | 122 (51.9) | 92 (59.0) | 27 (39.7) | **0.008** |
| Concomitant immunomodulating therapy – no. (%)Systemic corticosteroidsm/Othern | 37 (15.7)30 (12.8)/7 (3.0) | 24 (15.4)20 (12.8)/4 (2.6) | 13 (19.1)10 (14.7)/3 (4.4) | 0.490.70/0.47 |

AD, atopic dermatitis; BMI, body mass index; IQR, interquartile range; SD, standard deviation; No., number; ISCED, International Standard Classification of Education; EASI, Eczema Area Severity Index; NRS, Numerical Rating Scale; POEM, Patient-Oriented Eczema Measure; DLQI, Dermatology Life Quality Index. Significant p-values displayed in bold. Missing data: 1n=15, 2n=5, 3n=33, 4n=14, 5n=16, 6n=11, 7n=1, 8n=51-57, 9n=25, 10n=59, 11n=62,12n=59, 13n=64, 14n=22, 15n=20, 16n=58, 17n=53, analysis of NL data, 18n=56, analysis of NL data, 19n=16, 20n=2, 21n=10. a AD based on the U.K. working party’s diagnostic criteria: n=133 (NL), n=102 (UK), b Excluding patients <18 years, c <18 years: ISCED of parents, f physician-diagnosed, g positive patch test; never tested (n=24), tested negative (n=15), unknown (n=12) or missing (n=87), h patient-reported, i patient-reported food allergy was confirmed by a physician diagnosis; patient-reported food allergy (n=131), j first degree family member with at least one of the following allergic diseases: AD, asthma, allergic rhinoconjunctivitis, atopic eye disease or other, k open-label extension study, l dimethyl fumarate (n=1), rituximab (n=1), m predniso(lo)ne, n ciclosporin (n=3), long-term clarithromycin (n=1), methotrexate (n=1), mycophenolate mofetil (n=1), ciclosporin and dupilumab concomitantly (n=1).

**Table 2. Effectiveness of dupilumab, methotrexate and ciclosporin according to skin type**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  |  |  | Baseline score | Follow-up score | p-value† | .Δ score |
| Dupilumab | **EASI** | **Mean score dark skin type (SD)** | 24.2 (13.0) | 7.5 (7.1) | **<0.001** | 16.7 (13.0) |
|  |  | **Mean score light skin type (SD)** | 18.0 (13.0) | 8.3 (7.5) | **<0.001** | 9.7 (11.0) |
|  |  | **p-value** Δ **difference‡** |  |  |  | **0.032** |
|  | **POEM** | **Mean score dark skin type (SD)** | 20.2 (6.0) | 10.1 (6.0) | **<0.001** | 10.1 (6.4) |
|  |  | **Mean score light skin type (SD)** | 19.9 (5.7) | 10.5 (6.8) | **<0.001** | 9.4 (6.8) |
|  |  | **p-value** Δ **difference‡** |  |  |  | 0.33 |
|  | **DLQI** | **Mean score dark skin type (SD)** | 15.6 (6.8) | 6.2 (7.6) | **<0.001** | 9.4 (8.5) |
|  |  | **Mean score light skin type (SD)** | 14.1 (6.7) | 5.7 (5.7) | **<0.001** | 8.4 (7.3) |
|  |  | **p-value** Δ **difference‡** |  |  |  | 0.54 |
|  | **NRS** | **Mean score dark skin type (SD)** | 6.9 (1.8) | 3.5 (2.2) | **<0.001** | 3.4 (2.3) |
|  |  | **Mean score light skin type (SD)** | 7.2 (2.3) | 3.4 (2.7) | **<0.001** | 3.7 (3.0) |
|  |  | **p-value** Δ **difference‡** |  |  |  | 0.99 |
| Methotrexate | **EASI** | **Mean score dark skin type (SD)** | 12.9 (9.2) | 7.2 (3.9) | **0.048** | 5.7 (7.4) |
|  |  | **Mean score light skin type (SD)** | 19.0 (13.2) | 7.9 (5.8) | **0.019** | 11.0 (14.7) |
|  |  | **p-value** Δ **difference‡** |  |  |  | 0.52 |
|  | **POEM** | **Mean score dark skin type (SD)** | 13.8 (9.5) | 10.5 (7.8) | 0.32 | 3.2 (8.5) |
|  |  | **Mean score light skin type (SD)** | 18.5 (9.6) | 10.9 (6.8) | **0.007** | 7.5 (8.4) |
|  |  | **p-value** Δ **difference‡** |  |  |  | 0.19 |
|  | **DLQI** | **Mean score dark skin type (SD)** | 9.9 (6.9) | 5.0 (3.5) | 0.051\* | 4.9 (5.9) |
|  |  | **Mean score light skin type (SD)** | 12.6 (8.3) | 7.0 (7.5) | **0.011** | 5.6 (6.0) |
|  |  | **p-value** Δ **difference‡** |  |  |  | 0.26 |
|  | **NRS** | **Mean score dark skin type (SD)** | 5.2 (3.1) | 3.8 (2.3) | 0.17 | 1.3 (2.1) |
|  |  | **Mean score light skin type (SD)** | 5.9 (2.9) | 3.2 (2.2) | **0.037** | 2.7 (3.2) |
|  |  | **p-value** Δ **difference‡** |  |  |  | 0.74 |
| Ciclosporin | **EASI** | **Mean score dark skin type (SD)** | 23.2 (14.7) | 10.3 (14.4) | 0.054\* | 12.9 (8.3) |
|  |  | **Mean score light skin type (SD)** | 21.3 (8.5) | 8.2 (11.4) | **<0.001** | 13.1 (6.9) |
|  |  | **p-value** Δ **difference‡** |  |  |  | 0.98 |
|  | **POEM** | **Mean score dark skin type (SD)** | 19.8 (9.3) | 13.5 (8.4) | 0.29 | 6.2 (9.7) |
|  |  | **Mean score light skin type (SD)** | 19.6 (6.4) | 8.0 (9.3) | **0.008** | 11.6 (9.9) |
|  |  | **p-value** Δ **difference‡** |  |  |  | 0.39 |
|  | **DLQI** | **Mean score dark skin type (SD)** | 16.2 (9.0) | 6.8 (7.3) | 0.12 | 9.5 (8.7) |
|  |  | **Mean score light skin type (SD)** | 13.8 (5.7) | 3.1 (2.4) | **<0.001** | 10.7 (5.9) |
|  |  | **p-value Δ difference‡** |  |  |  | 0.36 |
|  | **NRS** | **Mean score dark skin type (SD)** | 7.2 (2.2) | 5.0 (2.9) | 0.25 | 2.2 (3.2) |
|  |  | **Mean score light skin type (SD)** | 7.1 (2.2) | 2.4 (2.5) | **0.005** | 4.7 (3.7) |
|  |  | **p-value** Δ **difference‡** |  |  |  | 0.63 |

Mean scores (SD) for dark and light skin type at baseline and follow-up (6 months dupilumab, 6 months methotrexate, 3 months ciclosporin), and the corresponding differences for each skin type. Δ-score: reduction in score between baseline and follow-up. The p-value Δ difference‡ between the Δ-scores for light and dark skin type was assessed according to a multivariable linear model, corrected for age, baseline score, follicular eczema, allergic contact dermatitis and previous use of phototherapy. †Paired t-tests for comparison between baseline and follow-up. Number of patients per treatment group: dupilumab: dark: n=35, light: n=90; methotrexate: dark: n=10, light: n=15; ciclosporin: dark: n=4, light: n=11. EASI, Eczema Area and Severity Index (0-72); POEM, Patient-Oriented Eczema Measure (0-28); DLQI, Dermatology Life Quality Index (0-30); NRS, Numerical Rating Scale (0-10). Significant p-values displayed in bold. \*, borderline significant. The minimal clinically important difference for improvement is a decrease of 6.6 points for EASI, 3.4 points for POEM, 3.3 points for DLQI, and 2.7 points for NRS pruritus.

**Supplementary material 1**

Criteria were defined for the assessment of morphological characteristics. Presence of dermatitis was assessed based on the location on the skin surface using size cut-offs for the lesions.\*

**FLEXURAL ECZEMA (select ‘yes’ only if one of the localizations named below is affected):** Ο Yes Ο No

If yes, which areas are involved:

* Ο Skin folds around one or both eye(s), patch ≥1cm
* Ο Neck (front), patch ≥1cm
* Ο Flexure of the elbow(s), one or both sides patch ≥1cm
* Ο Flexure of the knee(s) (popliteal fossae), one or both legs patch ≥1cm
* Ο Front of ankle(s), one or both sides patch ≥1cm

**NON-FLEXURAL ECZEMA (select ‘yes’ only if one of the localizations named below is affected):** Ο Yes Ο No

If yes, which areas are involved:

* Ο Face, at least one non-flexural patch ≥2cm
* Ο Legs, both sides patch ≥2cm
* Ο Extensor of the knees, both sides patch ≥2cm
* Ο Extensor of the elbows, both sides patch ≥2cm
* Ο Arms, both sides patch ≥2cm
* Ο Hands, both sides patch ≥2cm
* Palmar hyperlinearity: Ο Yes Ο No
* Pompholyx (syn. vesicular eczema): Ο Yes Ο No
* History of Pompholyx (syn. vesicular eczema): Ο Yes Ο No

**OTHER CLINICAL CHARACTERISTICS**

* Discoid (syn. nummular) eczema (≥5 circular patches in total, each patch ≥2cm diameter):

Ο Yes Ο No

* Nodular prurigo (≥5 palpable nodules of the skin from long-term scratching (usually on the legs or arms), ≥1cm diameter each): Ο Yes Ο No
* Follicular eczema (widespread eczematous hair follicle involvement, more commonly seen in darker skin types): Ο Yes Ο No
* Keratosis pilaris (thickening around the base of hair follicles over upper arms, thighs or cheeks):

Ο Yes Ο No

* Erythroderma (≥90% BSA involvement): Ο Yes Ο No
* Ichthyosis (widespread fine scale predominantly affecting the non-flexural areas of the limbs and body): Ο Yes Ο No
* Clinical suspicion of skin infection: Ο Yes Ο No

If Yes: Ο Bacterial | Ο Viral | Ο Fungal

Sample taken: Ο Yes Ο No

\* Reference: Williams HC, Flohr C. So How Do I Define Atopic Eczema? A Practical manual for researchers wishing to define atopic eczema. Available from: <https://www.nottingham.ac.uk/~mzzfaq/dermatology/eczema/contents.html>

**Supplementary material 2**

**The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Item No.** | **STROBE items** | **Location in manuscript where items are reported** | **RECORD items** | **Location in manuscript where items are reported** |
| **Title and abstract**  |
|  | 1 | (a) Indicate the study’s design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found | (a) Abstract (b) Abstract | RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included.RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract.RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract. | * 1. Abstract
	2. Methods - study design & setting
	3. Not applicable
 |
| **Introduction** |
| Background rationale | 2 | Explain the scientific background and rationale for the investigation being reported | Introduction  |  |  |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | Introduction  |  |  |
| **Methods** |
| Study Design | 4 | Present key elements of study design early in the paper | Methods – study design |  |  |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | Methods – setting |  |  |
| Participants | 6 | *(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up*Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls*Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants*(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed*Case-control study* - For matched studies, give matching criteria and the number of controls per case | (a) Methods – participants(b) Not applicable | RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided.RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage. | 6.1. Methods – participants6.2. Not applicable6.3. Not applicable |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable. | Methods – participants & variables & definition of treatment endpoint | RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided. | 7.1. Not applicable |
| Data sources/ measurement | 8 | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | Methods – variables & definition of treatment endpoint |  |  |
| Bias | 9 | Describe any efforts to address potential sources of bias  | Methods – statistical analyses & Discussion |  |  |
| Study size | 10 | Explain how the study size was arrived at | Methods – participants |  |  |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why | Methods – statistical analyses |  |  |
| Statistical methods | 12 | (a) Describe all statistical methods, including those used to control for confounding(b) Describe any methods used to examine subgroups and interactions(c) Explain how missing data were addressed(d) *Cohort study* - If applicable, explain how loss to follow-up was addressed*Case-control study* - If applicable, explain how matching of cases and controls was addressed*Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy(e) Describe any sensitivity analyses | (a-c) Methods – statistical analyses(d-e) Not applicable |   |  |
| Data access and cleaning methods |  |  |  | RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population.RECORD 12.2: Authors should provide information on the data cleaning methods used in the study. | 12.1. Not applicable12.2. Not applicable  |
| Linkage |  |  |  | RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided. | 12.3. Not applicable |
| **Results** |
| Participants | 13 | (a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed)(b) Give reasons for non-participation at each stage.(c) Consider use of a flow diagram | Results – baseline patient characteristics | RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram. | 13.1. Methods – study design & setting & participants |
| Descriptive data | 14 | (a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders(b) Indicate the number of participants with missing data for each variable of interest(c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount) | (a-b) Results – baseline patient characteristics(c) Figure legends |  |  |
| Outcome data | 15 | *Cohort study* - Report numbers of outcome events or summary measures over time*Case-control study* - Report numbers in each exposure category, or summary measures of exposure*Cross-sectional study* - Report numbers of outcome events or summary measures | Results – effectiveness according to skin type & concomitant therapy during follow-up & safety & treatment discontinuation & differences in morphological phenotypes |  |  |
| Main results | 16 | (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included(b) Report category boundaries when continuous variables were categorized(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | (a) Methods – statistical analyses(b-c) Not applicable |  |  |
| Other analyses | 17 | Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses | Not applicable |  |  |
| **Discussion** |
| Key results | 18 | Summarise key results with reference to study objectives | Discussion |  |  |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | Discussion | RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported. | Not applicable |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | Discussion |  |  |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | Discussion |  |  |
| **Other Information** |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | Funding sources |  |  |
| Accessibility of protocol, raw data, and programming code |  |  |  | RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code. | Not applicable |

\*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.

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**Supplementary table 1**

**Supplementary table 1a. Overview of potentially related adverse events during dupilumab treatment, including action, course and type**

|  |
| --- |
| Dupilumab treatment |
|  | **All patients (n=168)** | **Light skin type (n=121)** | **Dark skin type (n=42)** |
| Number of patients with adverse events – no. (%)\* | 31 (18)\*\* | 22 (18) | 8 (19) |
| Total number of adverse events – no. | 43\*\* | 25 | 17 |
| Action on adverse event – no.Treatment discontinuation Adjustment of treatment scheduleNo treatment adjustment | 9¶7 27 | 46 15 | 5 111 |
| Course of adverse event – no.Recovered/resolvedRecovered/resolved with sequelaeNot recovered/resolvedFatalUnknown | 1202308 | 401902 | 80405 |
| Type of adverse event† – no.Eye disorders* (Kerato)conjunctivitis
* Sicca complaints
* Blepharitis
* Epiphora
* Combined diagnoses‡

General disorders and administration site conditions* Malaise
* Hot flushes
* Injection site reaction

Musculoskeletal and connective tissue disorders* Arthralgia

Infections and infestations* Cold sores

Skin and subcutaneous tissue disorders* Perioral dermatitis
* Facial redness

Psychiatric disorders* Depressed mood

Respiratory, thoracic and mediastinal disorders* Maxillary sinusitis
* Pneumonia

Gastrointestinal disorders* Palatal ulcer

Nervous system disorders* Migraines
 | 26\*\*932111\*\*51222222211222111111 | 207221800000011211002110000 | 52100251222211000220001111 |
| Serious adverse events – no. | 0 | 0 | 0 |
| Median (IQR) number of days between start dupilumab and event§ | 35 (14-84) | 59.5 (17.75-181) | 22.5 (1-61.75) |

*Only events with a relatedness being categorized as possible, probable, very likely or definite (NL) and likely or confirmed (UK) were included. In the Netherlands, severe AEs were registered, defined as any undesirable experience resulting in referral to another specialist, prescription of medication (excl. antihistamines and indifferent treatments), treatment schedule adjustments or discontinuation, or causing considerable interference with usual activities, whether or not considered related to this treatment. In the U.K., mild, moderate and severe AEs were registered according to the clinical judgment of the investigator. Events that resulted in death, were life-threatening, required (prolonging of) hospitalization, resulted in persistent or significant disability, or congenital anomaly or birth defect, were considered serious AEs.*

No., number; \*\*, missing skin type: n=1; †, categorized according to Medical Dictionary for Regulatory Activities (MedDRA) terminology categories; \*, Chi-squared test for comparison between light and dark skin type: p=0.74; §, missing data: n=8, Mann-Whitney Test for comparison between light and dark skin type: p=0.07.

**Supplementary table 1b. Overview of potentially related adverse events during methotrexate treatment, including action, course and type**

|  |
| --- |
| Methotrexate treatment |
|  | **All patients (n=65)** | **Light skin type (n=37)** | **Dark skin type (n=22)** |
| Number of patients with adverse events – no. (%)\* | 10 (15) | 5 (14) | 5 (23) |
| Total number of adverse events – no. | 20 | 10 | 10 |
| Action on adverse event – no.Treatment discontinuationAdjustment of treatment scheduleNo treatment adjustment | 1523 | 901 | 622 |
| Course of adverse event – no.Recovered/resolvedRecovered/resolved with sequelaeNot recovered/resolvedFatalUnknown | 10¶0505 | 60400 | 40105 |
| Type of adverse event† – no.General disorders and administration site conditions* Fatigue
* Malaise

Gastrointestinal disorders* Nausea
* Combination of complaintsa

Respiratory, thoracic and mediastinal disorders* Common cold
* Dry cough
* Dyspnea

Skin and subcutaneous tissue disorders* Erysipelas
* Molluscum contagiosum

Investigations* Liver function abnormalities

Hepatobiliary disorders* Hepatic pain

Immune system disorders* Urticaria

Nervous system disorders* Headache

Psychiatric disorders* Confusional state
 | 54151431112111111111111 | 33030300001010000111111 | 21121131111101111000000 |
| Serious adverse events – no. | 0 | 0 | 0 |
| Median (IQR) number of days between start dupilumab and event§ | 3 (0-136.25) | 0 (0-0) | 29 (3-351) |

No., number; †, categorized according to Medical Dictionary for Regulatory Activities (MedDRA) terminology categories; ¶, 8 of the events were in combination with other event(s) reason for treatment discontinuation;\*, Chi-squared test for comparison between light and dark skin type: p=0.36; §, missing data: n=12, Mann-Whitney Test for comparison between light and dark skin type: p=0.057.

**Supplementary table 1c. Overview of potentially related adverse events during ciclosporin treatment, including action, course and type**

|  |
| --- |
| Ciclosporin treatment |
|  | **All patients (n=26)** | **Light skin type (n=19)** | **Dark skin type (n=7)** |
| Number of patients with adverse events – no. (%)\* | 9 (35) | 7 (37) | 2 (29) |
| Total number of adverse events – no. | 16 | 10 | 6 |
| Action on adverse event – no.Treatment discontinuationAdjustment of treatment scheduleNo treatment adjustment | 11¶14 | 703  | 411 |
| Course of adverse event – no.Recovered/resolvedRecovered/resolved with sequelaeNot recovered/resolvedFatalUnknown | 303010 | 10306 | 20004 |
| Type of adverse event† – no.Nervous system disorders* Epilepsy
* Headache

Vascular disorders* Hypertension

Gastrointestinal disorders* Abdominal pain
* Nausea

Musculoskeletal and connective tissue disorders* Muscle strain

Skin and subcutaneous tissue disorders* Hypertrichosis

Psychiatric disorders* Libido loss

Investigations* Renal function disorder

Immune system disorders* Eczema herpeticum
 | 413332112222111111 | 202331100011111111 | 211001012211000000 |
| Serious adverse events – no. | 0 | 0 | 0 |
| Median (IQR) number of days between start dupilumab and event§ | 115.9 (6-171) | 57 (3-280.5) | 93.5 (16-93.5) |

No., number; †, categorized according to Medical Dictionary for Regulatory Activities (MedDRA) terminology categories; ¶, 5 of the events were in combination with other event(s) reason for treatment discontinuation;\*, Chi-squared test for comparison between light and dark skin type: p=0.69; §, missing data: n=9, Mann-Whitney Test for comparison between light and dark skin type: p=0.70.

**Supplementary table 2**

**Supplementary table 2a. Concomitant immunomodulating therapy during dupilumab treatment**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Concomitant immunomodulating therapy - dupilumab** | **All patients (n=168)** | **Light skin type (n=121)** | **Dark skin type (n=42)** | **p-value** |
| **Patients who used systemic immunomodulating therapy from baseline until the end of study – no. (%)** Type of therapy: Prednisonea, \* CiclosporinMethotrexate  Mycophenolate mofetil | **8 (4.8)**4 (2.4)2 (1.2)1 (0.6)1 (0.6) | **5 (4.1)**2 (1.7)2 (1.7)0 (0)1 (0.8) | **3 (7.1)**2 (4.8)0 (0)1 (2.4)0 (0) | 0.35 |
| **Patients who discontinued systemic immunomodulating therapy after starting dupilumab – no. (%)** Type of therapy: Prednisonea Ciclosporin Duration in days - median (IQR)1 | **20 (11.9)**19 (11.3)1 (0.6)25.0 (7.0-49.0) | **14 (11.6)**14 (11.6)0 (0.0)24 (6.0-46.0) | **6 (14.3)**5 (11.9)1 (2.4)35 (11.0-123.5) | 0.290.38 |
| **Patients who started systemic immunomodulating therapy after starting dupilumab – no. (%)**Type of therapy: PrednisoneaMethotrexate Mycophenolate mofetil2 | **3 (1.8)**1 (0.6)1 (0.6)1 (0.6) | **2 (1.7)**1 (0.8)1 (0.8)**-** | **0 (0)**0 (0)0 (0)**-** | 0.63 |

No., number; IQR, interquartile range; a or prednisolone; \*, one patient discontinued systemic corticosteroids for 14 days and then restarted until the end of study; missing data: 1n=1: light skin type n=1, 2 n=1: skin type missing; In total, 31 patients used systemic therapy after starting dupilumab. The three patients who started using concomitant systemic therapy used this for 17 days during follow-up (n=1, prednisone) and until end of study (n=2). One of the patients who discontinued received hydrocortisone for a period of 24 weeks during dupilumab treatment because of a steroid withdrawal syndrome after stopping prednisone. During dupilumab treatment one patient has received a prednisone course of 7 days for a maxillary sinusitis in combination with a pneumonia and another prednisone course of 3 days for an exacerbation of AE between visits.

**Supplementary table 2b. Concomitant immunomodulating therapy during methotrexate treatment**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Concomitant immunomodulating therapy - methotrexate** | **All patients (n=65)** | **Light skin type (n=37)** | **Dark skin type (n=22)** | **p-value** |
| **Patients who used systemic immunomodulating therapy from baseline until the end of study – no. (%)** Type of therapy: Prednisonea, 1 Ciclosporin Clarithromycin followed by prednisone | **3 (4.6)**1 (1.5)1 (1.5)1 (1.5) | **2 (5.4)**-1 (2.7)1 (2.7) | **0 (0)****-**0 (0)0 (0) | 0.55 |
| **Patients who discontinued systemic immunomodulating therapy after starting methotrexate – no. (%)** Type of therapy:  Prednisonea Dupilumab Ciclosporin Duration in days – mean ± SD | **6 (9.2)**4 (6.2)1 (1.5)1 (1.5)39.5 ± 32.3 | **3 (8.1)**2 (5.4)1 (2.7)0 (0.0)41.0 ± 23.4 | **3 (13.6)**2 (9.1)0 (0.0)1 (4.5)38.0 ± 45.3 | 0.290.92 |
| **Patients who started systemic immunomodulating therapy after starting** **methotrexate – no. (%)** Type of therapy: OtherDupilumab Prednisonea | **4 (6.2)**2 (3.1)1 (1.5)1 (1.5) | **3 (8.1)**1 (2.7)1 (2.7)1 (2.7) | **1 (4.5)**1 (4.5)0 (0)0 (0) | 0.73 |

No., number; SD, standard deviation; a or prednisolone; 1 n=1: skin type missing; In total, 13 patients used systemic immunomodulating therapy after starting methotrexate. Clarithromycin was used as anti-inflammatory treatment followed by prednisone in one patient. Three patients who started using concomitant systemic therapy used this for 669 days of follow-up (therapy: other), unknown (n=1) and until end of study (n=2). One patient received a prednisone course for 10 days between visits, one week after starting methotrexate treatment, because of an exacerbation of AE.

**Supplementary table 2c. Concomitant immunomodulating therapy during ciclosporin treatment**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Concomitant immunomodulating therapy - ciclosporin** | **All patients (n=26)** | **Light skin type (n=19)** | **Dark skin type (n=7)** | **p-value** |
| **Patients who used systemic immunomodulating therapy from baseline until the end of study – no. (%)** Type of therapy: Prednisonea Dupilumab | **2 (7.7)**1 (3.8)1 (3.8) | **2 (10.5)**1 (5.3)1 (5.3) | **0 (0)**0 (0)0 (0) |  |
| **Patients who discontinued systemic immunomodulating therapy after starting ciclosporin – no. (%)**  Type of therapy: Prednisonea  Duration in days - median (IQR)1 | **3 (11.5)**3 (11.5)14.5 (3.0-26.0) | **3 (15.8)**3 (15.8)14.5 (3.0-26.0)) | **0 (0)**0 (0)0 (0) |  |
| **Patients who started systemic immunomodulating therapy after starting** **ciclosporin – no. (%)** Type of therapy: Prednisonea and methotrexate Prednisonea | **2 (7.7)**1 (3.8)1 (3.8) | **2 (10.5)**1 (5.3)1 (5.3) | **0 (0)**0 (0)0 (0) |  |

No., number; SD, standard deviation; a or prednisolone; missing data: 1n=1: light skin type n=1; In total, 7 patients used systemic therapy after starting ciclosporin. One patient started using concomitant systemic therapy after respectively 63 and 14 days of follow-up: prednisone (for 56 days), methotrexate (until end of study). During ciclosporin treatment one patient was treated with prednisone for a course of 10 days between visits.

**Supplementary table 3. Overview of treatment discontinuation**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Treatment discontinuation** | **All patients**  | **Light skin type**  | **Dark skin type** | **p-value** |
| **Patients who discontinued treatment with dupilumab during the study – no. (%)** Reasons: Side-effects Ineffectiveness Ineffectiveness in combination with side-effects Child wish Elective surgery Compliance Patient choice1 Other | **23 (13.7)**9 (5.4)7 (4.2)1 (0.6)2 (1.2)1 (0.6)1 (0.6)1 (0.6)1 (0.6) | **13 (10.7)**4 (3.3)6 (5.0)0 (0)2 (1.7)0 (0)0 (0)-1 (0.8) | **9 (21.4)**5 (11.9)1 (2.4)1 (2.4)0 (0)1 (2.4)1 (2.4)-0 (0) | 0.08 |
| **Patients who discontinued treatment with methotrexate during the study – no. (%)** Reasons: Side-effects1 Ineffectiveness Ineffectiveness in combination with side-effects Effectiveness Patient choice1 Other | **20 (30.8)**11 (6.5)4 (6.2)1 (1.5)2 (3.1)1 (1.5)1 (1.5) | **9 (11.6)**5 (24.3)3 (8.1)1 (2.7)0 (0)-0 (0) | **9 (40.1)**5 (22.7)1 (4.5)0 (0)2 (9.1)-1 (4.5) | 0.18 |
| **Patients who discontinued treatment with ciclosporin during the study – no. (%)** Reasons: Side-effects Ineffectiveness Ineffectiveness in combination with side-effects Effectiveness | **12 (46.2)**5 (19.2)5 (19.2)1 (3.8)1 (3.8) | **9 (47.4)**4 (21.1)3 (15.8)1 (5.3)1 (5.3) | **3 (42.9)**1 (14.3)2 (28.6)0 (0)0 (0) | 0.84 |

No., number; 1 n=1: skin type missing; 3 patients were lost to follow-up in the dupilumab group, 3 in the methotrexate group and 2 in the ciclosporin group.

**Supplementary figures**

**Supplementary figure 1. Difference in Patient-Oriented Eczema Measure (POEM) from baseline (delta POEM) over time for each treatment group**

**Supplementary figure 2. Difference in Dermatology Life Quality Index (DLQI) from baseline (delta DLQI) over time for each treatment group**

**Supplementary figure 3. Difference in Numerical Rating Scale (NRS) peak pruritus past 24 hours from baseline (delta NRS) over time for each treatment group**

Estimated mean differences in scores from baseline (including 95% confidence interval) for our linear mixed-effects models, with continuous values for time and time displayed in weeks and corrected for age, baseline score, follicular eczema, allergic contact dermatitis and previous use of phototherapy, in patients with atopic dermatitis. Higher delta scores indicate greater improvement of disease activity and/or burden. The median follow-up duration for the outcome measurements varied from 38 to 46 weeks (IQR: 14-74 weeks) for dupilumab, from 17 to 19 weeks (IQR: 1-47 weeks) for methotrexate and from 15 to 17 weeks (IQR: 0-32 weeks) for ciclosporin. Dupilumab: n=168 at baseline (light skin types (LST): n=121; dark skin types (DST): n=42), n=125 at 6 months (LST: n=90; DST: n=35). Methotrexate: n=65 at baseline (LST: n=37; DST: n=22), n=25 at 6 months (LST: n=15; DST: n=10). Ciclosporin: n=26 at baseline (LST: n=19; DST: n=7), n=15 at 3 months (LST: n=11; DST: n=4).