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Effectiveness and safety of dupilumab in the treatment of atopic dermatitis in children (6–11 years): data from a French multicentre retrospective cohort in daily practice

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To cite this version:

Audrey Lasek, Nathalia Bellon, Sylvain Mallet, Ève Puzenat, Anne-Claire Bursztejn, et al.. Effectiveness and safety of dupilumab in the treatment of atopic dermatitis in children (6–11 years): data from a French multicentre retrospective cohort in daily practice. Journal of the European Academy of Dermatology and Venereology, 2022, 36 (12), pp.2423 - 2429. 10.1111/jdv.18450 . hal-03903398

HAL Id: hal-03903398

https://univ-rennes.hal.science/hal-03903398v1

Submitted on 16 Dec 2022

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Title: Effectiveness and safety of dupilumab in the treatment of atopic dermatitis in children (6-11 years): data from a French multicenter retrospective cohort in daily practice

Keywords: atopic dermatitis; dupilumab; children; daily practice

Manuscript word count: 2419 words

Abstract word count: 268

Figures: 2

Tables: 5

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/jdv.18450

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Funding sources: None

Conflicts of Interest:

A. Lasek has paid activities as a consultant, advisor, or speaker for Sanofi, AbbVie, and Lilly.

J.Mazereeuw-Hautier is a consultant for Sanofi and Abbvie.

E.Mahé has paid activities as a consultant, advisor, or speaker for Sanofi, AbbVie, and Janssen-Cilag.

Other authors have no conflicts of interest to disclose.

Acknowledgement: The patients/patients' guardians in this manuscript have given written informed consent to the publication of their case details.

Data availability statement:

This study was approved by the CNIL (*Commission Nationale de l'Informatique et des Libertés*). Non-opposition to the use of their de-identified records was obtained for this non-interventionnal study, in accordance with French legislation.

Abbreviations used:

AD: atopic dermatitis

SE: Side effect

DFR: dupilumab facial redness

IGA/ Investigator global assessment

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IQR: interquartile range

SCORAD: Scoring atopic dermatitis

SCORAD50 : SCORAD score improvement of at least 50%

SCORAD75: SCORAD score improvement of at least 75%

TCS: topical corticosteroids

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Abstract

Background: Dupilumab is the first biotherapy available for the treatment of moderate-to-severe childhood atopic dermatitis (AD).

Objective: The aim of this study was to evaluate the effectiveness and safety of dupilumab in daily practice.

Methods: Patients aged 6 to 11, who had received a first dose of dupilumab were included in this multicenter retrospective cohort study. The primary endpoint was change in SCORAD after 3 months of treatment. Secondary endpoints were change in IGA score at 3 months, proportion of patients with SCORAD50 and SCORAD75, description of adverse events and proportion of children in our cohort who would be excluded from pivotal phase 3 clinical trial.

Results: 80 patients were included. After 3 months of treatment, there was a significant decrease in SCORAD (mean: 21.8 ± 13.8 vs 53.9 ± 18.5; p<0.0001) and IGA (1.3 ± 0.8 vs 3.5 ± 0.7; p<0.0001). Conjunctivitis was observed in 11.3%(n=9/80); 3 patients experienced dupilumab facial redness (DFR); 17.5% (n=14/80) reported injection site reactions; 6.3% (n=5/80) discontinued treatment. 61.2 % (n=49/80) children were ineligible in the phase 3 trial.

Limitations: There is no control group. Because it was a real life study based on information from patient medical records in a French multicenter cohort, we cannot rule out the presence of reporting bias generated by the use of patient reported characteristics and missing information.
Conclusion: These real-life data confirm the efficacy and safety of dupilumab in children with moderate to severe AD extended to dyshidrosis and atopic prurigo but it also revealed a lower frequency of DFR and conjunctivitis. However, administration in injectable form may be a barrier in this age group.

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INTRODUCTION

Atopic dermatitis (AD) is one of the most common skin disorders in children and the leading contributor to the global burden of skin disease.(1,2) In children with moderate-to-severe AD, skin lesions often involve a large body surface area (BSA), and the related pruritus, sleep deprivation, activity restriction, reduced school performance, depression, and anxiety have a greater impact on quality-of-life (QOL) for patients and their family (3).

AD begins before the age of 5 years in more than 85% of patients and persists into adulthood in half of the cases. (4). Despite the chronic nature of AD, treatment in children is often limited to short-term topical corticosteroids (TCS), and topical calcineurin inhibitors (5-7). Although other systemic agents have been used off-label such as cyclosporine (not approved before 16 years of age in France), methotrexate, or azathioprine, the risk of serious adverse events (AE) associated with these agents and the lack of high-level evidence of long-term efficacy makes them especially difficult to manage for this age group requiring biology monitoring (8). Systemic therapies are offered only as a last resort for the most intractable cases, resulting in a large unmet need for children whose disease is inadequately controlled with topical therapy. Dupilumab (Dupixent®) is a fully human monoclonal antibody derived from VelocImmune that blocks the shared receptor component of interleukin-4 and interleukin-13. Dupilumab clinical trials have shown that these cytokines are key and central drivers of multiple type 2 inflammatory diseases. Dupilumab is approved for use in the United States and European Union and other countries for adults and adolescents with severe AD,

severe asthma with evidence of type 2 inflammation or eosinophilia, and adults with chronic rhinosinusitis and nasal polyps. Dupilumab significantly improves symptoms and quality of life in adults and adolescents with moderate-to-severe AD, with an acceptable safety profile. (9-17)

The results of a phase 3 trial of dupilumab with concomitant topical corticosteroids in children aged 6-11 years with severe AD inadequately controlled with topical therapies have been reported (11). Dupilumab was effective on symptoms and quality of life and well tolerated in children. The safety profile was consistent with that observed in adults and adolescents. Dupilumab was approved in Europe in November 2020 for children aged 6-11 years with severe AD inadequately controlled with topical therapies, and use was available by temporary authorization use (ATU). Few data are available with regard to the efficacy and safety of dupilumab in real life conditions.

This study was designed to assess the effictiveness and safety of dupilumab in children from 6 to 11 years with AD in real life, in a French multicenter retrospective cohort. We also evaluated the eligibility of our children for the published phase 3 clinical trial.

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METHODS

Study design and population

In this study, we evaluated the data collected in a French multicenter retrospective cohort conducted by the research group of *Société Française de Dermatologie Pédiatrique* (SFDP) and by the *Groupe de Recherche sur l'eczéma atopique* (GREAT) of the French Society of Dermatology. Consecutive patients aged 6 to 11 years with a diagnosis of AD who received at least one injection of dupilumab between August 2018 and May 2021 were eligible for this study.

Ethical aspects

This study was approved by the CNIL (*Commission Nationale de l'Informatique et des Libertés*). Non-opposition to the use of their de-identified records was obtained for this non-interventionnal study, in accordance with French legislation.

Data Collection

A standardized questionnaire was sent to members of the GREAT and SFDP groups. The following information was collected from patient medical records: demographic variables, comorbidities, AD clinical features, previous treatments, date of introduction and dose of dupilumab, severity scores (SCORAD and investigator global assessment (IGA)) at baseline and during follow up. We evaluated the frequency and reasons of discontinuation of dupilumab at the end of follow up.

Outcomes

SCORAD and IGA were evaluated at baseline, 3 and 6 months when available. The primary outcome was the evolution of SCORAD at 3 months compared with baseline. The secondary outcome was the SCORAD at 6 months compared with baseline. We evaluated the frequency of children who achieved a 50% (SCORAD 50) or 75% (SCORAD 75) SCORAD reduction after 3 or 6 months of treatment.

We also evaluated IGA at 3 and 6 months compared with baseline and the frequency of IGA 0 or 1 (clear or nearly clear) at 3 and 6 months.

Side effects

Sides (SE) were collected. SEs were defined as the occurrences of any adverse medical condition during the treatment period. Eosinophilia was defined as a blood eosinophil count >500/mm3.

Serious SE (SSE) included SEs that resulted in death; were life-threatening; required hospitalization or prolongation of a current hospitalization ; resulted in persistent or significant disability or incapacity; or required intervention to prevent permanent impairment or damage.

Assessment of eligibility

The eligibility for clinical trials for each patient was assessed retrospectively, based on criteria used in the phase 3 trial evaluating the efficacy and safety of dupilumab with concomitant topical corticosteroids in children aged 6-11 years with severe atopic dermatitis (12); "*Key inclusion criteria were children age 6-11 years with AD (American Academy of Dermatology consensus criteria) diagnosed ≥1 year before screening; Investigator's Global Assessment (IGA) score of 4, Eczema Area and Severity Index (EASI) score ≥21, affected BSA ≥15%, weekly averaged baseline worst itch score (Peak Pruritus Numerical Rating Scale [NRS]) ≥4; weight ≥15 kg; and documented history of inadequate response to topical AD medication within 6 months prior to baseline.*"

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Statistical analysis

Quantitative data were expressed as means ± standard deviation, and qualitative data as frequency and percentages. Comparisons of means were performed using Student's t-test. A p-value below 0.05 was considered statistically significant. Statistical analyses were performed using the R software, version 3.4.3.

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RESULTS

Baseline Characteristics

The study population comprised 80 patients from 21 hospitals in France. There were 46 girls (57.5%) and the mean age was 9.3 years. The characteristics of the population and disease are detailed in table 1.

Medical history

Patients had a variety of associated morbidities: atopic morbidities included asthma (n=35/80, 43,8%), allergic rhinitis (n=28/80, 35%) and food allergy (n= 23/80, 28,8%).

Atopic dermatitis

The mean age of onset of AD was 12.5 months (SD 20.8); 74/80 children (92.5%) had a classic diffuse form of AD, 7.5% (n=6) had either atopic nodular prurigo (n=3) or severe palmoplantar dyshidrosis (n=3).

Baseline scorad was 53,9 ± 18,5 and baseline IGA was 3.5 ± 0.7; baseline Child DLQI was performed only in 10 patients with a median of 8.5; 67/71 (94.3%) patients had an IGA score of 3 to 4, and 4/71 (5.6%) had IGA score of 1 to 2. 39 children had an eosinophilia > 500 /mm3 (mean: 1457/mm3) prior to dupilumab treatment.

Treatments for AD

Systemic treatment prior to dupilumab was prescribed in 38/80 children (47.5%).

Dupilumab effectiveness: Table 2

The mean age at dupilumab initiation was 9.1 years. Mean follow up was approximately 6 months. After 3 months of treatment, there was a significant decrease in SCORAD (median 21.8 ± 13.8 at 3 months vs. 53.9 ± 18.5 at baseline; p<0.0001) and a significant decrease in IGA (1.3 ± 0.8 at 3 months vs. 3.5 ± 0.7 in baseline; p<0.0001); 66.7% of children (n = 38/57) had reached an IGA of 0-1 at 3 months.

44 children of 61 (74.6%) had SCORAD50 at 3 months, 11 of 61 at 6 months (73.3%). 13/61 children (22%) had SCORAD75 at 3 months, 4/15 at 6 months (26.6%).

AD flares

On dupilumab, 31 children experienced AD flares. The management of flares was accomplished by the use of topical treatments: TCS or tacrolimus. Three flares were reported as head and neck dermatitis (Figure 1).

Dupilumab safety: Table 3

10/80 children (12.5%) experienced a noninfectious ophtalmologic SE, including 9 conjunctivitis (11,3%)(Figure 1 Severe conjunctivitis in a 9 year old boy on Dupilumab), 2 blepharitis (2.5%) and 2 ocular pruritus.

The proportion of patients with eosinophilia (>500 / mm3) was not significantly higher at 3 months of treatment (n = 40) than before initiation (n = 39), however eosinophilia above 5000 / mm3 was

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detected in 3 patients at 3 months. Fourteen (17%) children reported injection site reactions or pain. Three children reported transient dupilumab-induced facial redness.(figure 1: Dupilumab facial redness)

Discontinuation of dupilumab: Table 4

Five children (6,3%) stopped treatment; including 2 children who discontinued due to injection-related pain.

Eligibility: Table 5

Of the 80 patients included, 49 (61.2%), were ineligible due to at least one or more exclusion criteria for the phase 3 trial. Of these 49 patients, 33 were ineligible due to disease severity (SCORAD <50 or IGA <4) and 6 due to the clinical type of AD (atopic prurigo or palmoplantar dyshydrosis)

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DISCUSSION

This retrospective observational study confirmed the real life effectiveness of dupilumab in real life and its safety in children aged 6 to 11 years with AD. The strengths of this real life study are that the patients were not selected (as they are in clinical trials) and they represented a sample of the pediatric population aged 6 and 11 year treated with dupilumab in France. Results were similar to those obtained in the clinical trials. The results of a phase 3 trial of dupilumab with concomitant TCS in children aged 6-11 years with severe AD inadequately controlled with topical therapies have been reported (12). Dupilumab and TCS are effective and well tolerated in children with severe AD, and significantly improved quality of life. Among children treated with Dupilumab + tcs , 29.5% achieved IGA scores of 0 or 1 at 3 months. In our study, after 3 months of treatment, there was a significant decrease in SCORAD and IGA: 68.4% of children (n = 39) had reached 0-1 IGA at 3 months.

We observed a lower rate of conjunctivitis with dupilumab (11,3%) in children 6-11 years old children, compared with clinical trial results in adults (38%) (17), similar to adolescents 10.3% (14) and to children 6.7% with dupilumab q4w and 14.8% with dupilumab 100/200mg 2QW (12). We did not observe a higher proportion of patients with eosinophilia at follow up compared with baseline. However, we did observe an increase of eosinophils count in these patients. Only 3 patients had eosinophilia > 5000/ mm3, leading to discontinuation of treatment. In one case, dupilumab was not effective, and in another dupilumab was effective in body symptoms but lead to facial redness. None of our patients showed clinical signs of internal organ involvement due to eosinophil infiltration. The mechanisms underlying dupilumab-induced hypereosinophilia remain unknown, but it is often associated with asthma and allergic rhinitis (17).

Dupilumab facial redness (DFR) is a side effect characterized by the paradoxical onset or worsening of facial dermatitis reported in approximately 10% of adults receiving dupilumab and is less frequent in children (18). In this study only 3 children (3%) experienced DFR. DFR may occur more frequently in post pubertal children rather than prepubertal children (35% vs 14%) with a

higher incidence with increasing age (19). The etiology of this eruption is currently unclear. One hypothesis is that DFR is a seborrheic malassezia-induced dermatitis which is consistent with the lower rate of seborrheic dermatitis in younger children. However, antifungal topics are not very effective (20).

Children with severe AD inadequately controlled with topical therapies have limited therapeutic options. Immunosuppressive treatments as cyclosporine or methotrexate do not have legal authorization (AMM) in France to treat severe AD in children; however, these molecules are used in clinical practice (8). We observed in our study an important proportion of patients who did not receive systemic treatment before dupilumab (n=42, 52.5%). In the future, the use of prior systemic treatments in severe AD in children aged 6-11 years will certainly decrease.

Another frequently reported side effect in children is pain at the injection site (n=14), which in our study led to discontinuation of treatment in 2 children. This injection site pain could be avoided by systematically prescribing a local anesthetic before injection in children. According to our experience, some children prefer using the syringe rather than the injection pen, which is more painful for them.

Phase 3 clinical trials of biotherapies are designed for a selected population. For example, in a recent real life cohort of children with psoriasis, it was shown that more than 50% of children included in the cohort were ineligible for randomized controlled trial. Thus, efficacy and safety results from phase 3 clinical trials in selected populations may not sufficiently reflect what is observed in real life, hence the need for results from real life cohort studies (22). Our study investigated whether children treated for atopic dermatitis with dupilumab in real life practice would differ from children in the original phase 3 trial from Paller (12). We found that 61.2% of patients in our cohort would not be eligible for the clinical trial. Instead of lower disease severity, IGA score and SCORAD were lower than required, probably because children had no treatment washout before starting dupilumab. The second reason was the presence of other forms than classic AD, mainly palmoplantar dyshidrosis and atopic prurigo (23,24). In daily practice in France, moderate to severe AD is characterized by SCORAD

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>50 and IGA >4. (European Task Force on Atopic Dermatitis. Severity scoring of atopic dermatitis: the SCORAD index. Consensus Report of the European Task Force on Atopic Dermatitis. Dermatology 1993;186:23-31). However, these parameters have been shown to have limited relevance in real life conditions and are insufficient to determine the severity of AD. In addition, in clinical trials designed for drug approval, all previous treatments are withdrawal from patients and they don't have severe comorbidities. Pretrial wash out periods and allowing only specific "mild" medication may lead to increase in disease severity resulting in artificially high EASI and IGA scores being recorded at the beginning of the clinical trial. In the real life, patients may have severe comorbidities and have previous treatments, clinicians don't let them get worse before starting a new treatment.

Our study has some limitations. Because it was a real life study based on information from patient medical records in a French multicenter cohort, we cannot rule out the presence of reporting bias generated by the use of patient reported characteristics and missing score data for 6-month follow-up.

CONCLUSION

These real-life data confirm the effectiveness and safety of dupilumab in children with moderate to severe AD extended to dyshidrosis and atopic prurigo but also showed a lower frequency of DFR and conjunctivitis than previous studies in adolescents and adults. However, administration in injectable form may be a barrier in this age group.

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Table 1. Characteristics of the 80 children, and of the atopic dermatitis (AD)

Children	
Gender, girls, n (%)	46 (57.5)
Age (y), mean ± SD	9.3 ± 2.0
BMI (kg.m^{-2}), mean ± SD	18.0 ± 3.7
Past history of HSV infection, n (%)	6 (7.5)
Family history of atopy, n (%)	
AD	42 (52.5)
Asthma	35 (43.8)
Rhinitis	28 (35.0)
Alimentary allergies	23 (28.8)
Atopic dermatitis	
Age at onset (m), mean ± SD	12.5 ± 20.8
Main clinical type, n (%)	
Classic AD	74 (92.5)
Palmoplantar dyshidrosis	3 (3.8)
Atopic prurigo	3 (3.8)
Previous eosinophilia > 500/mm^3, n (%)	40 (50.0)
Previous general treatments for AD, n (%)	
Cyclosporine	30 (37.5)
Methotrexate	21 (26.3)
Phototherapy	3 (3.8)
Omalizumab	1 (1.3)
Azathioprine	1 (1.3)
Acitretin [1]	5 (6.3)

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Dupilumab	
Age at onset (y), mean ± SD	9,1 ± 1,9
Duration of dupilumab (d), mean ± SD [2]	99.0 ± 107.2
Total cumulative years of dupilumab (y)	21.7

AD: atopic dermatitis; SD: standard deviation

[1] For atopic prurigo and palmoplantar eczema

[2] Include children who discontinued the treatment and those for which dupilumab is going

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Table 2. Evolution of severity scores

	Baseline		M3 ± 1 month		M6 ± 1 month	
Scores	N	Value	N	Value	N	Value
SCORAD, mean ± SD	76	53.9 ± 18.5	61	21.8 ± 13.8$^{<0.0001}$	15	20.5 ± 10.0$^{<0.0001}$
SCORAD 50, n (%)		-		44 (72.1)		11 (73.3)
SCORAD 75, n (%)		-		13 (21.3)		4 (26.7)
IGA, mean ± SD	71	3.5 ± 0.7	57	1.3 ± 0.8$^{<0.0001}$	12	0.8 ± 0.7$^{<0.0001}$
IGA 0-1, n (%)		0		38 (66.7)		8 (66.7)

N: number of children evaluated. IGA: investigator global assessment. SD: standard deviation
Superscript: p value if <0.5, in comparison to baseline. SCORAD 50 and SCORAD 75: reduction of SCORAD compared to baseline of 50% and 75% respectively

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Table 3. Adverse events in the 80 children treated by dupilumab, n (%)

AD flare	31 (38.8)
Head and neck form	3 (3.8)
Noninfectious ophtalmologic	10 (12.5)
Conjunctivitis	9 (11.3)
Blepharitis	2 (2.5)
Ocular pruritus	2 (2.5)
Eosinophilia	
$> 500/mm^3$	40 (50.0)
$> 5000/mm^3$	3 (3.8)
Redness head and neck	3 (3.8)
Pain or reaction injection site	14 (17.5)
Aphtous	1 (1.3)
Molluscum contagiosum	1 (1.3)
Diarrhea	1 (1.3)
Serious adverse events	0

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Table 4. Discontinuation of dupilumab

Number of children, n (%)	5 (6.3)
Duration before discontinuation (d), mean ± SD	302.6 ± 301.4
Causes of discontinuation, n (%)	
Adverse event	3 (60.0)
Eosinophilia	3
Injection pain	2
Inefficacy	1 (20.0)
Remission	1 (20.0)

SD: standard deviation

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Table 5. Eligibility of the 80 children in phase 3 study (12)

	Criteria not respected, N (%)
Age 6-11 years with AD	0
AD (American Academy of Dermatology consensus criteria)	6 (7.5)
AD diagnosed ≥ 1 year	0
IGA ≥ 4	33 (41.3)
Scorad > 50 [1]	35 (43.8)
Weight ≥ 15 kg	0
Inadequate response to topical AD medication	0
Affected BSA ≥15%,	Not evaluated
Weekly averaged baseline worst itch score ≥4;	Not evaluated
At least one criteria not respected	**49 (61.3)**

[1] Criteria in the clinical trial was EASI ≥ 21, that defined severe AD. Since EASI is not use in France, but SCORAD, we use the definition of severe AD, SCORAD > 50

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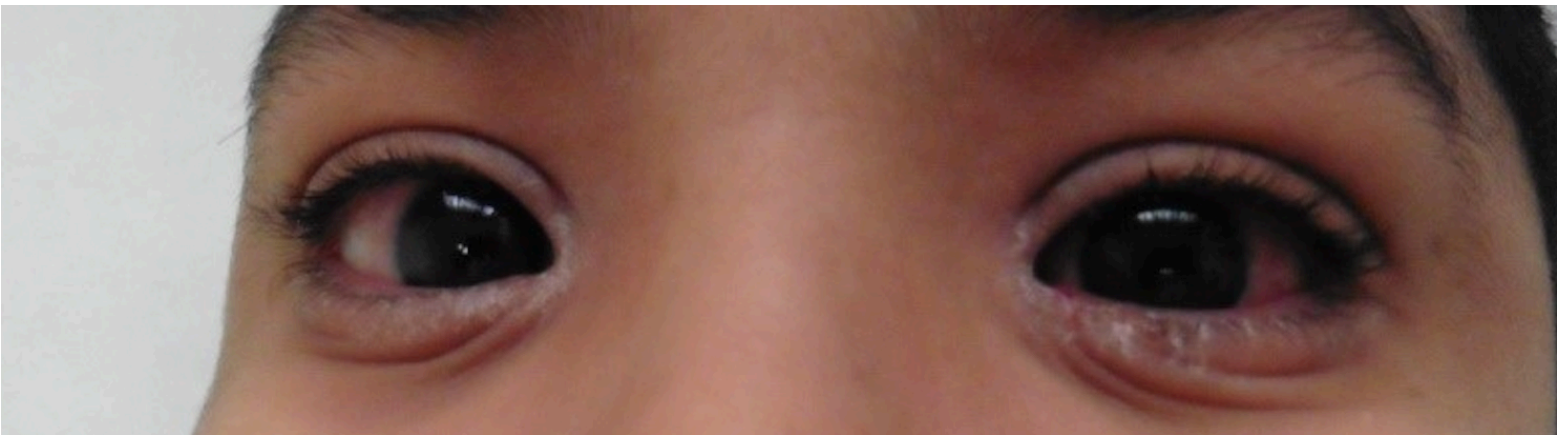

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Figure 2. Dupilumab facial redness

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