Atopic dermatitis update
Systemic therapy

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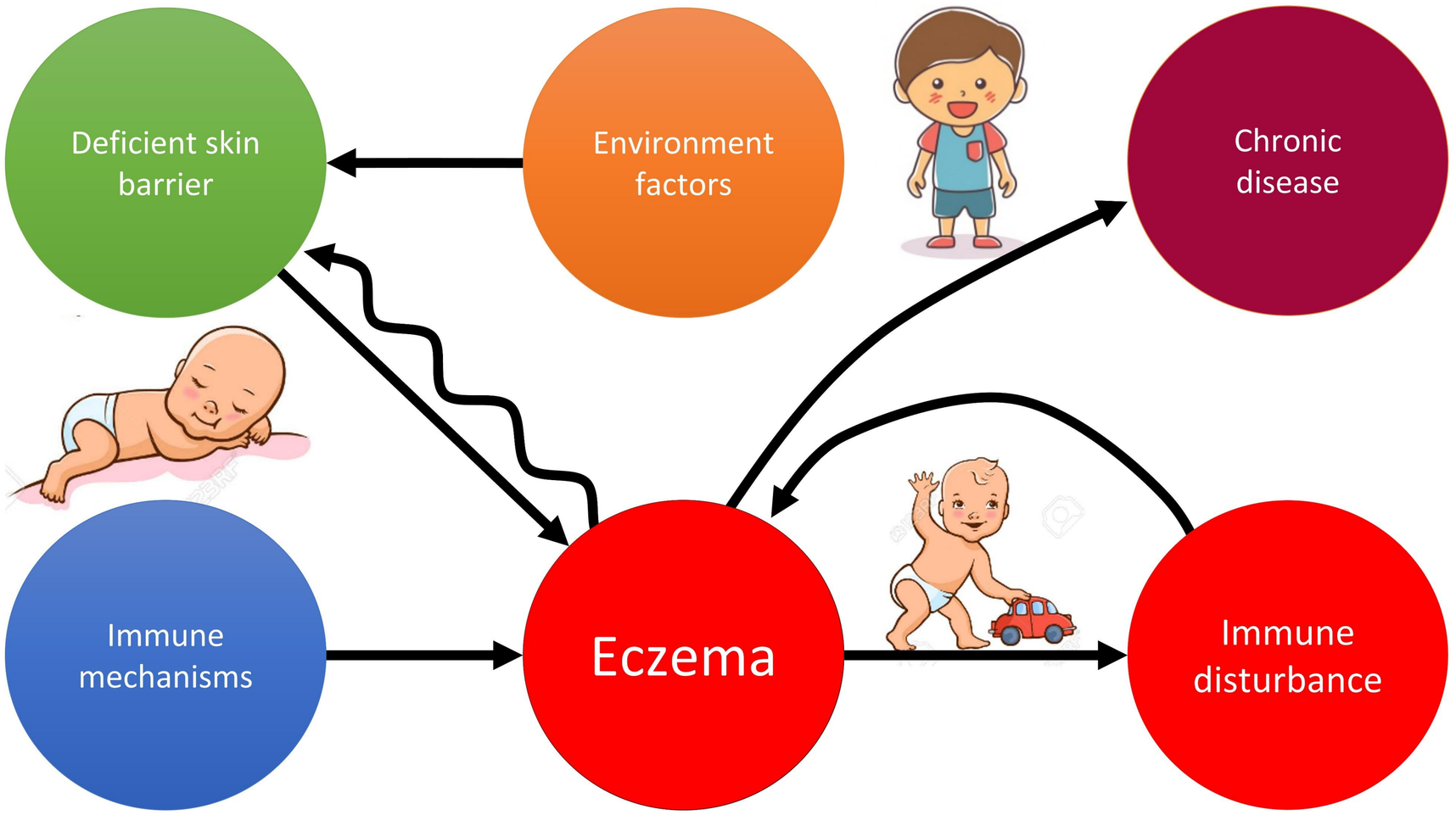
Conflicts of interest

- Speaker & Researcher
  - Viatris, Lilly, Pfizer, Abbvie, Sanofi, Almirall, Leo, Pierre Fabre, Mustela
- Advisor
  - Lilly, Pfizer

Who needs a systemic therapy?

Atopic dermatitis: skin disease or systemic disease



Mild atopic dermatitis lacks systemic inflammation and shows reduced nonlesional skin abnormalities

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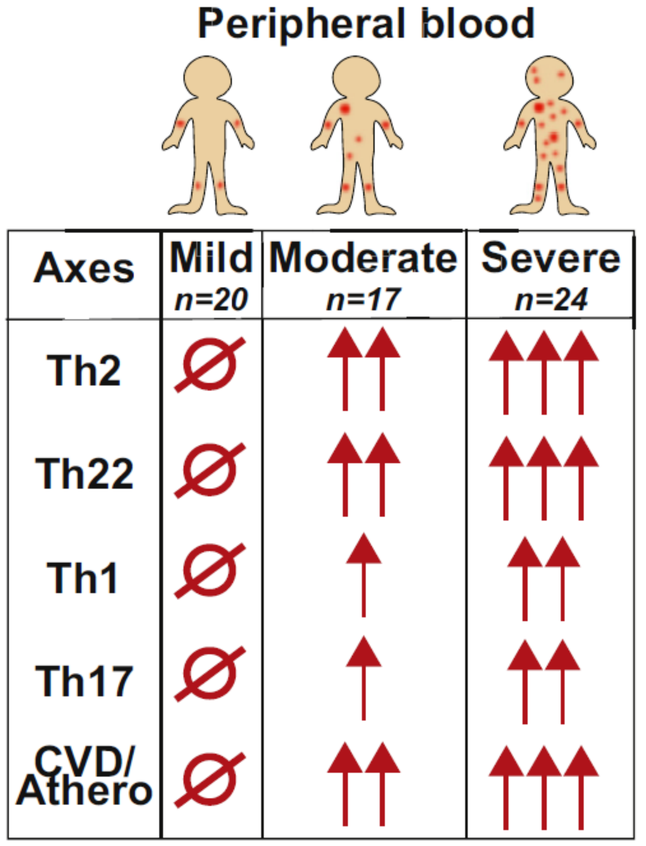
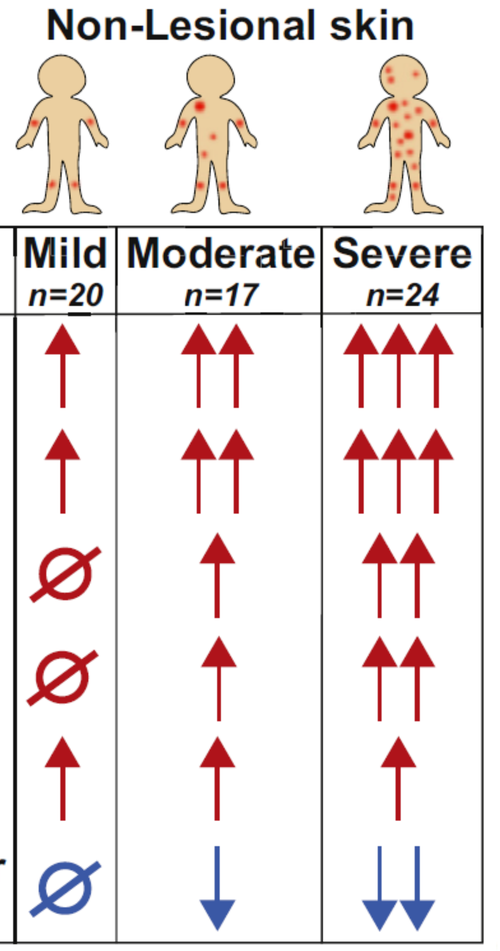
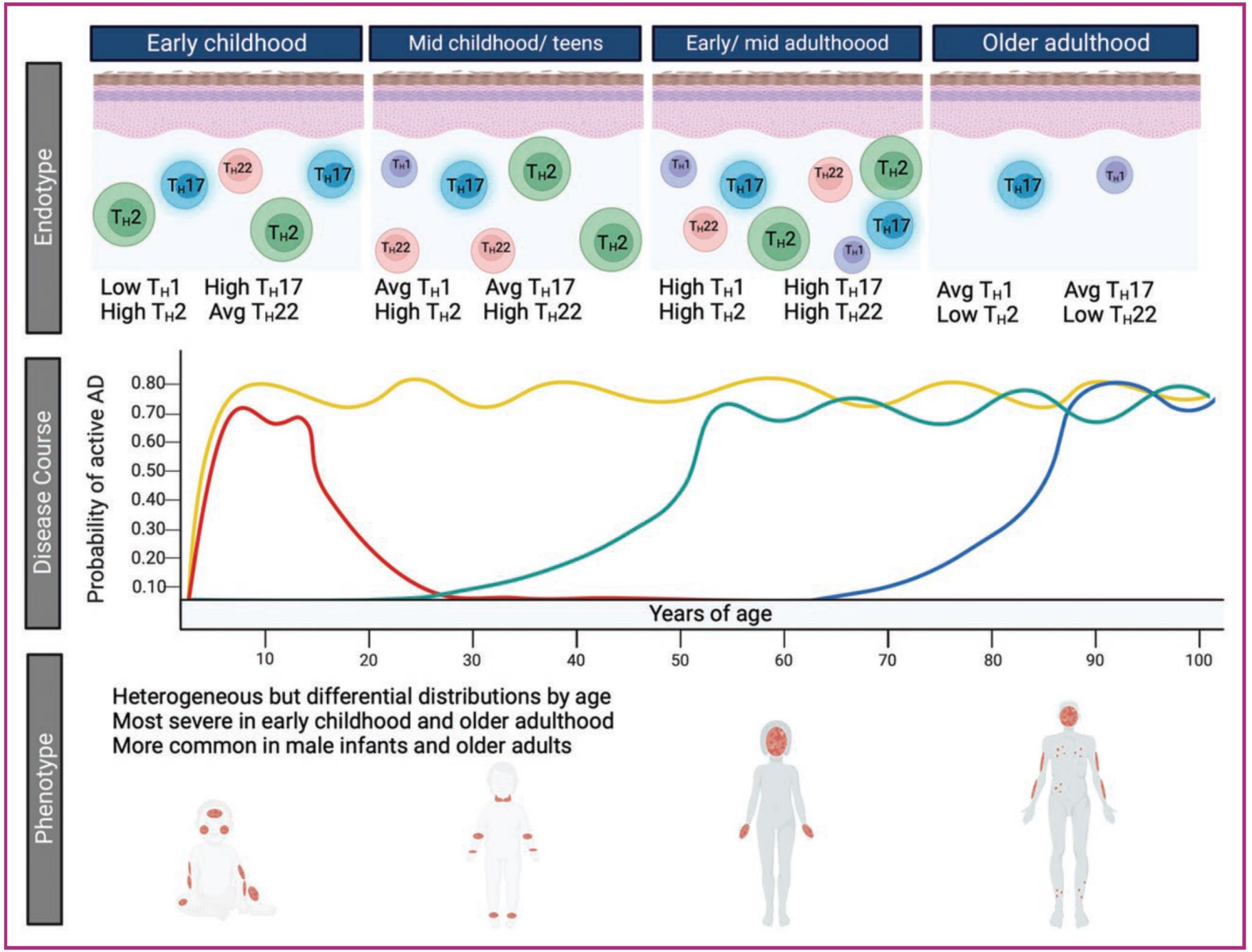
Overall, in this first study evaluating skin mRNA and cellular expression as well as blood proteomic expression of key immune and barrier biomarkers in mild or limited AD compared with in moderate and severe AD, we have demonstrated that although mild or limited disease retains universal pathogenic features of AD, such as T_H2/T_H22 cell activation, important cellular and molecular differences may distinguish patients with AD by severity. In contrast to patients with moderate and severe AD, who also have high levels of systemic inflammation, patients with mild or limited AD present with focal lesional inflammation that is potentially due to a relatively greater immune tolerance. Although patients with limited but locally significant disease lack systemic inflammation, they often have high disease burden and recurrence.[1,25-27,67] These patients may potentially benefit from targeted T_H2/T_H22 cell systemic treatment, which may perhaps provide a more sustained therapeutic response.

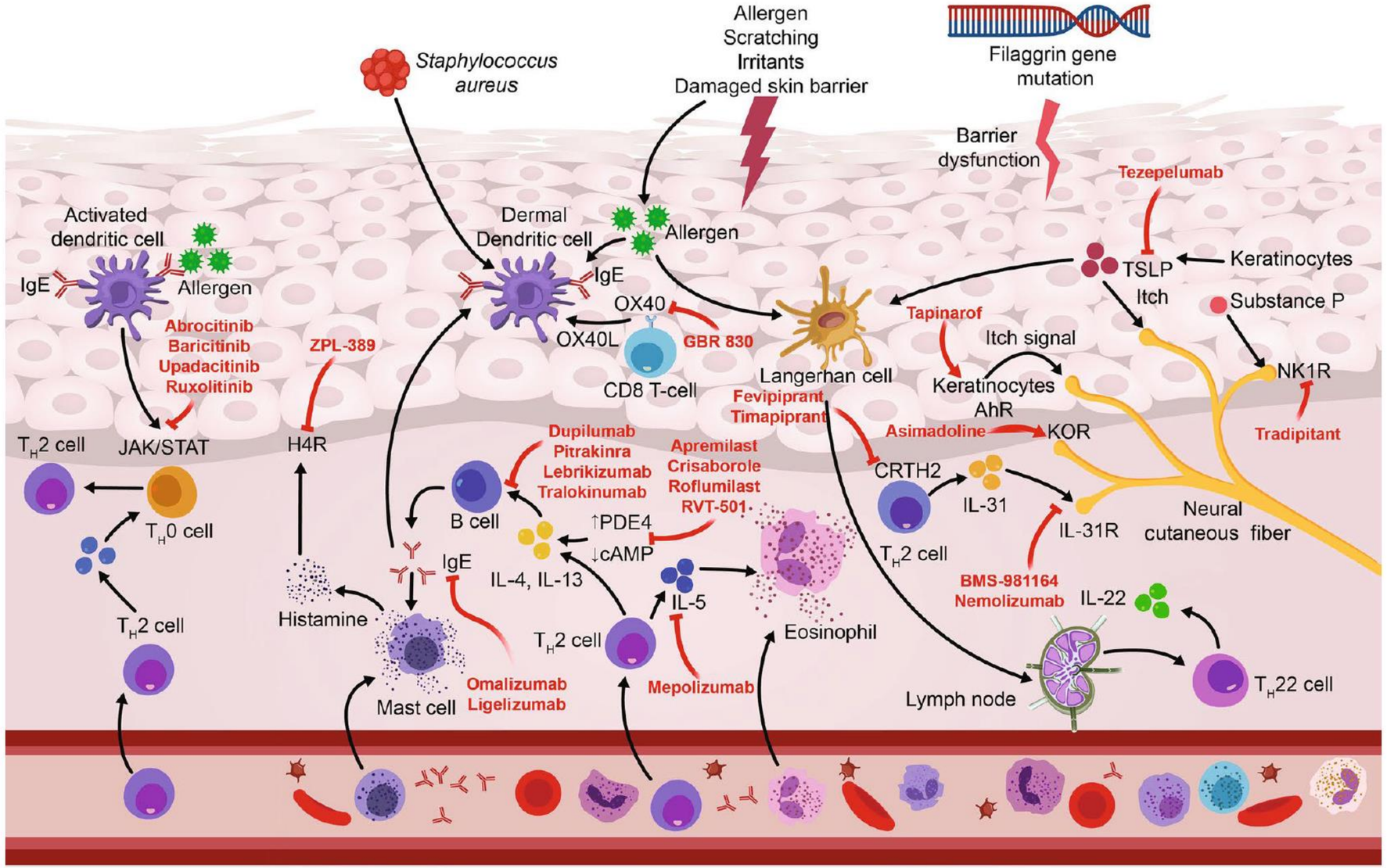




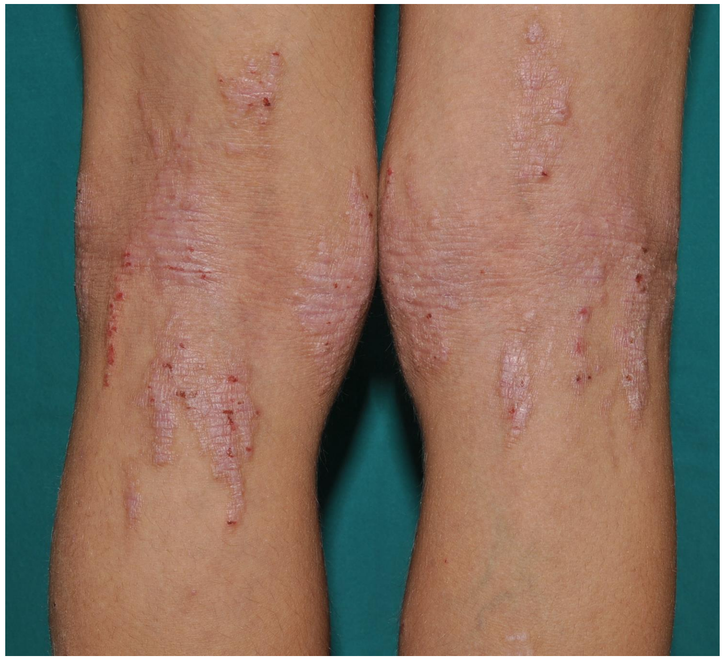


The pathomechanisms of AD may change trhoughout life
Heterogeneity of AD

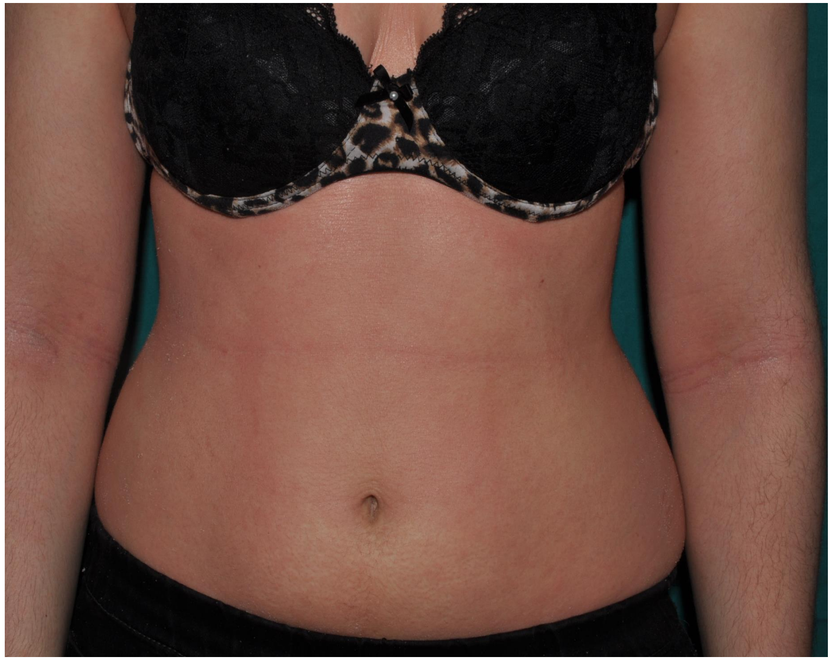
Understanding the complexity of AD



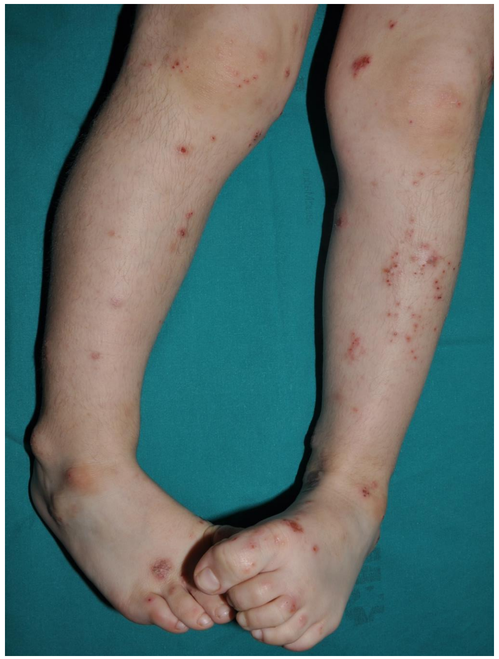
Heterogeneity of atopic dermatitis



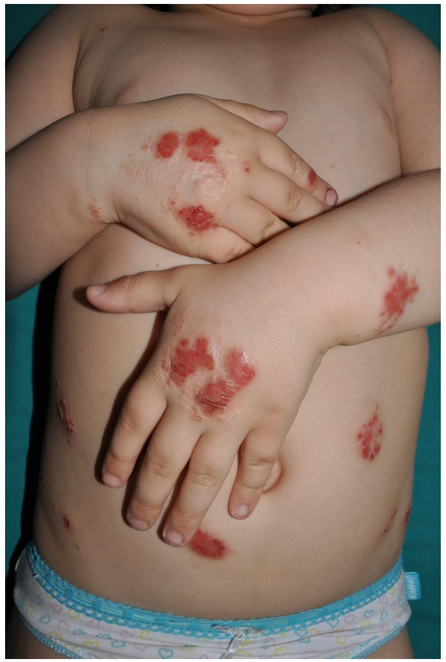
Mainly flexural



Erythroderma



Prurigo-eczema



Nummular

GUIDELINES

JEADV JOURNAL OF THE EUROPEAN ACADEMY OF DERMATOLOGY & VENEREOLOGY

European Guideline (EuroGuiDerm) on atopic eczema: Living update

A. Wollenberg[1,2,3] | M. Kinberger[4] | B. Arents[5] | N. Aszodi[2] | S. Barbarot[6] | T. Bieber[7] | H. A. Brough[8,9] | P. Calzavara-Pinton[10] | S. Christen-Zaech[11] | M. Deleuran[12] | M. Dittmann[4] | N. Fosse[13] | K. Gáspár[14] | L. A. A. Gerbens[15] | U. Gieler[16] | G. Girolomoni[17] | S. Gregoriou[18] | S. Holland[19] | C. G. Mortz[20] | A. Nast[4] | U. Nygaard[21] | E. M. Rehbinder[22,23] | J. Ring[24] | M. Rossi[10] | E. Serra-Baldrich[25] | D. Simon[26] | Z. Z. Szalai[27] | J. C. Szepietowski[28,29] | A. Torrelo[30] | T. Werfel[31] | R. N. Werner[4] | C. Flohr[32,33]

Abstract

The evidence- and consensus-based living guideline on atopic eczema was developed in accordance with the EuroGuiDerm Guideline and Consensus Statement Development Manual. The original EuroGuiDerm Guideline on atopic eczema was published in June 2022. Since then, the part of the guideline dealing with systemic therapy has been updated twice. This paper summarizes the results of the second update. Twenty-eight experts (including clinicians and patient representatives) from 12 European countries participated. The updated guideline provides guidance on which patients should be treated with systemic therapies, as well as recommendations and detailed information on each systemic drug. The systemic treatment options discussed in the guideline comprise conventional immunosuppressive drugs (azathioprine, ciclosporin, glucocorticosteroids, methotrexate and mycophenolate mofetil), biologics (dupilumab, lebrikizumab, nemolizumab and tralokinumab) and Janus kinase (JAK) inhibitors (abrocitinib, baricitinib and upadacitinib). Additionally, the updated guidelines address considerations for paediatric, adolescent, pregnant and breastfeeding patients. For all other aspects, please refer to the 2022 version.

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INTRODUCTION TO SYSTEMIC TREATMENT

The area of systemic therapy of AE has flourished during the last few years, as many new substances are marketed, licensed or in the last step of clinical development. The licensing programmes of the various new biologics and small molecules are providing much better levels of evidence than those available for the longer existing drugs due to more robust RCT evidence.

Systemic therapy of AE is deemed necessary if the signs and symptoms of AE cannot be controlled sufficiently with appropriate topical treatments and UV-light therapy. Systemic therapy can also be useful to reduce the total amount of topical corticosteroids (TCS) in patients who need large amounts of potent TCS over prolonged periods to control their AE.

Candidates for systemic treatment may be either patients with a high composite score such as a SCORAD above 50 (scale definition), or patients clinically failing to respond to an appropriately conducted topical therapy (functional definition), or patients unable to participate in normal daily life activities whilst following an adequate treatment regimen (social definition).

Local regulations may necessitate the use of scores such as physician-reported scores (e.g. EASI) in combination with patient reported outcomes (e.g. DLQI). Many other scores exist summarized and assessed by the HOME initiative that may also serve as a basis to classify disease severity.[7]

It must be highlighted that the indication to systemic treatment is a patient individual decision, and that a signs-only score, such as EASI, is not a sufficient tool to make a final decision on commencing systemic therapy to an individual patient.

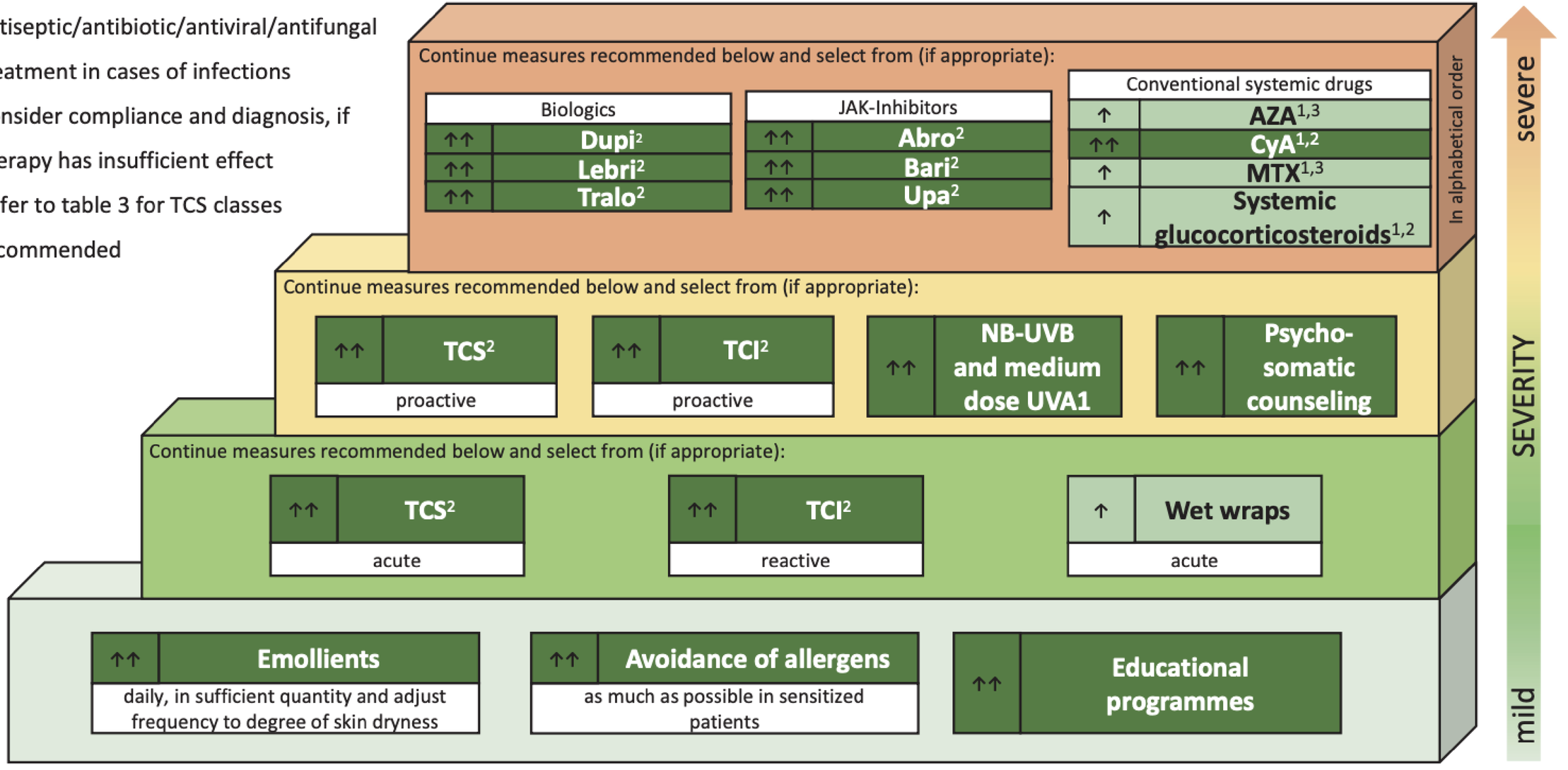
100 % agreement

Systemic treatment of AD

- When topical treatment is not enough
- When topical treatment is not convenient
- When topical treatment is harmful
- When there are repeated disease attacks
- When it shows continuous activity
- When there is a window opportunity for improvement

EuroGuiDerm Guideline on Atopic Eczema
Stepped-care plan for adults with atopic eczema

- Add antiseptic/antibiotic/antiviral/antifungal treatment in cases of infections
- Consider compliance and diagnosis, if therapy has insufficient effect
- Refer to table 3 for TCS classes recommended



Continue measures recommended below and select from (if appropriate):

Biologics	
↑↑	**Dupi**[2]
↑↑	**Lebri**[2]
↑↑	**Tralo**[2]

JAK-Inhibitors	
↑↑	**Abro**[2]
↑↑	**Bari**[2]
↑↑	**Upa**[2]

Conventional systemic drugs	
↑	**AZA**[1,3]
↑↑	**CyA**[1,2]
↑	**MTX**[1,3]
↑	**Systemic glucocorticosteroids**[1,2]

Continue measures recommended below and select from (if appropriate):

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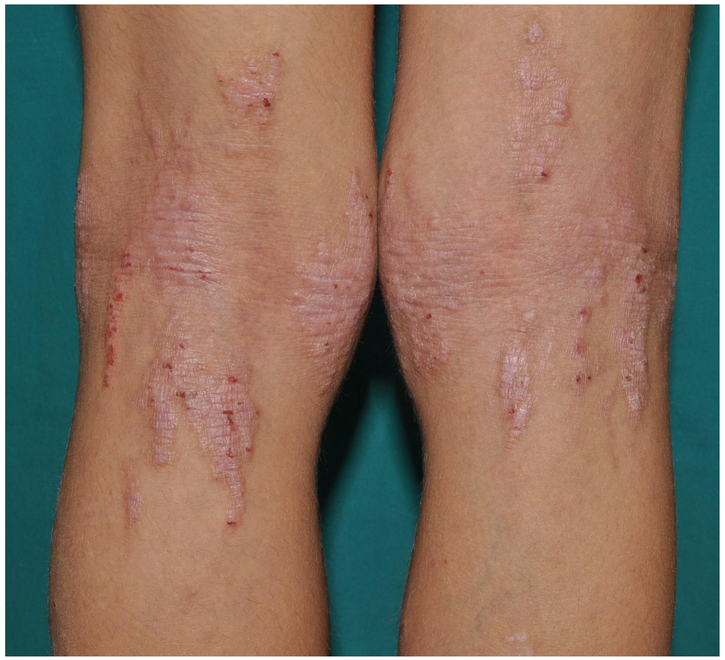
↑	**MTX**[1,3]
↑	**Systemic glucocorticosteroids**[1,2]

Is there a role for classical systemic drugs?



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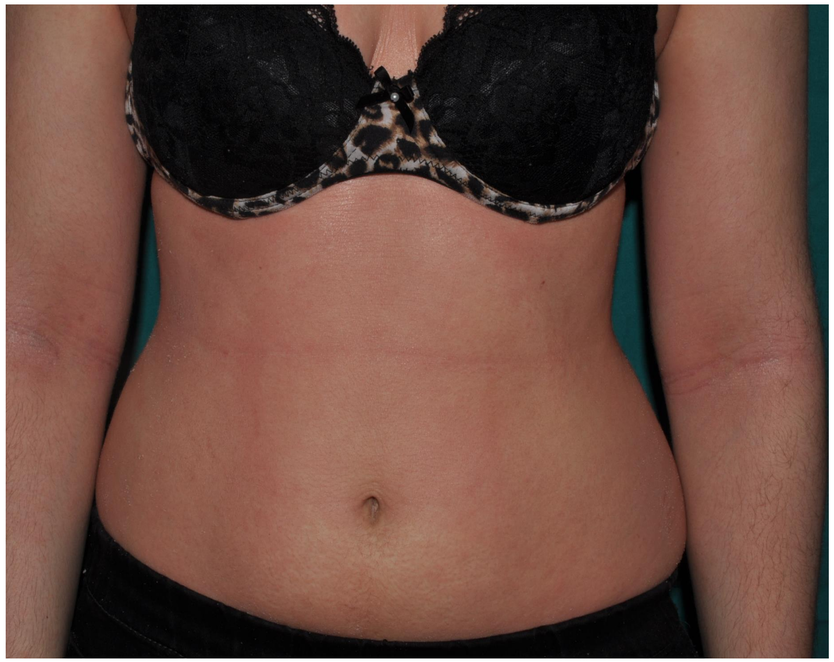
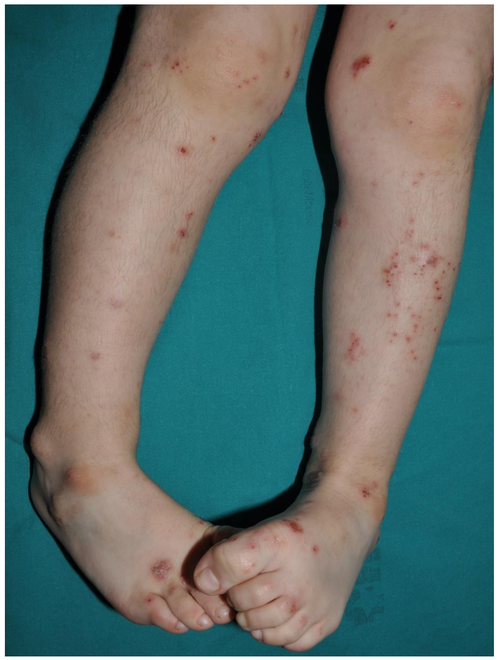


Erythroderma



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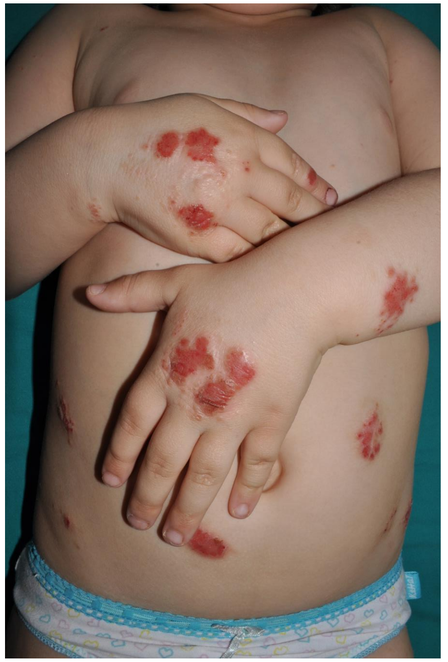


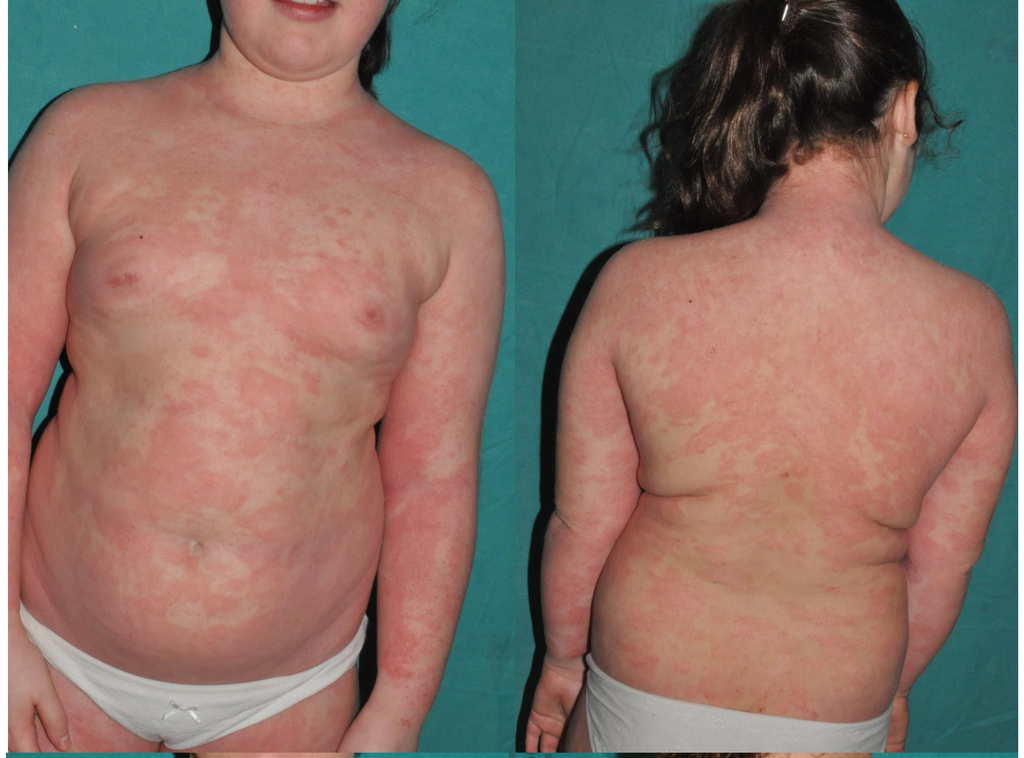
Nummular

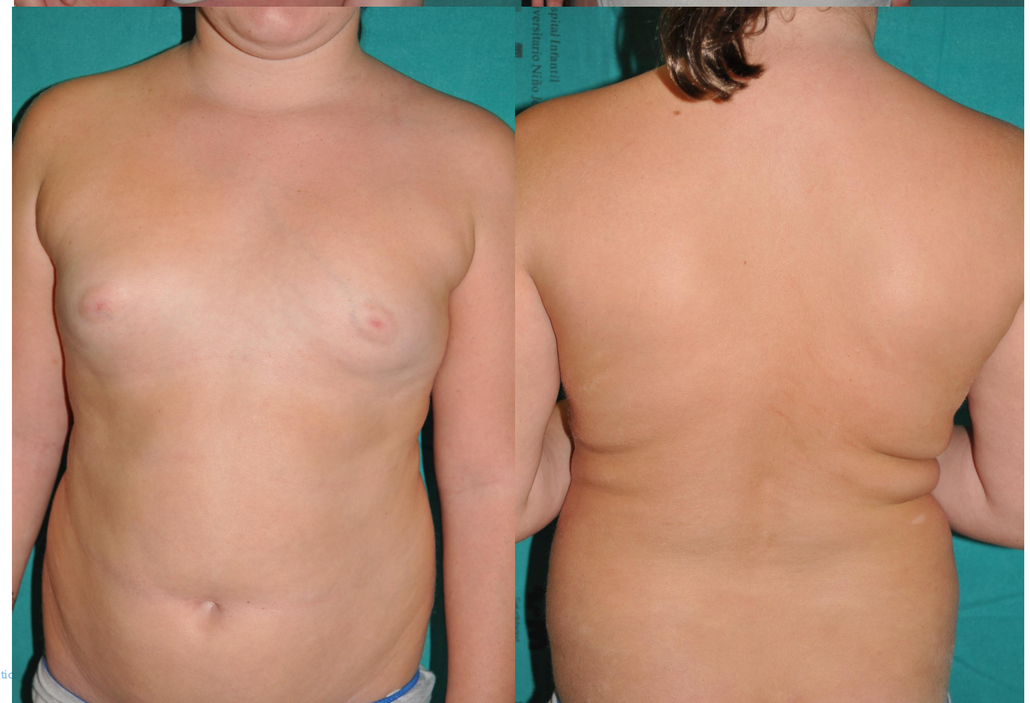
J Eur Acad Dermatol Venereol. 2016 Nov 29. doi: 10.1111/jdv.14066. [Epub ahead of print]

Cyclosporine A for severe atopic dermatitis in children. Efficacy and safety in a retrospective study of 63 patients

Hernández-Martín A[1], Noguera-Morel L[1], Bernardino-Cuesta B[2], Torrelo A[1], Pérez-Martin MA[2], Aparicio-López C[3], de Lucas-Collantes C[3]

	Berth-Jones	Zaki	Harper	Bunikowski	Haw	Sibbald	Our study
Study type	Prospective						
N	27	18	40	10	61	15	63
Age	2-16	3-16	2-16	2-16	9-68	5-15	8.4 ±3.6 yr,
Dosage	5 mg/kg/d	5-6 mg/kg/d	5 mg/kg/d	2.5 mg/kg/d	Mean 2.7 mg/kg/d	Mean 2.8 mg/kg/d	Mean 4.27 mg/kg/d
Length of treatment	6 weeks	4-12 weeks	1 year (continuous) vs 3 months (intermittent)	8 weeks	Mean 13.5 ± 8.4 months	Mean 10.9 ±2.7 months (1.5-21.6)	Median 4.6 months (1.5-21.6)
Time to efficacy assessment	6 weeks	NS	12 weeks	8 weeks	6 months	NS	4 weeks
Outcome	Complete or marked improvement 22/27 (81%)	Good to excellent 16/18 (88%)	Good or very good 30/40 (75%) (no statistically significant differences between groups)	Decrease of 50% of affected body surface in 9/10	Decrease of 50% in SCORAD index	Good 12/15 (80%)	Good to excellent 40/63 (64%)
Relapse	17/20 (85%)	16/18 (89%)	Continuous regimen: NS Short course: 17/19 (89%)	7/9 (78%)	100%	5/12 (42%)	21/40 (51%)
Disease-free period	Up to 6 months in 3 (11%) patients	Up to six months in 2 (11%) patients	Continuous regimen: NS Short course: 3 pts with sustained remission after a 3-month course (9%)	4 weeks	4.5±2.9 months	Min 15 months	Up to 6 months in 9 (14%) pts
Follow-up	10 months	Max 8 months	1 year	3 months	Min 6 months	Min 15 months	Up to 21 months
Side effects	Mild	Mild	57% mild, 37% moderate, 6% severe	Mild	Mild/moderate	Mild	Mild





Most children have good or excellent results (better if eosinophilia or egg allery are absent)

CyA acts rapidly in approximately 3-4 weeks. CyA therapy maintenance can be prolonged for 2 years safely

CyA is well tolerated, with few adverse effects, but needs close monitoring

CyA does not heal AD, and most patients witll recur, although some of them will experience long-term remissions

Methotrexate for severe nummular eczema in children: Efficacy and tolerability in a retrospective study of 28 patients

Nicole Knöpfel MD | Lucero Noguera-Morel MD | Angela Hernández-Martín MD | Antonio Torrelo MD

Abstract

Background/Objectives: Nummular eczema in children is a chronic condition characterized by pruritic coin-shaped eczematous lesions that affect any part of the body and often become exudative. Mid- to high-potency topical corticosteroids are considered the mainstay treatment, but there are limited data on the use of systemic therapy for nummular eczema in children. The objective of the current study was to evaluate the efficacy and safety of methotrexate in children with severe nummular eczema.

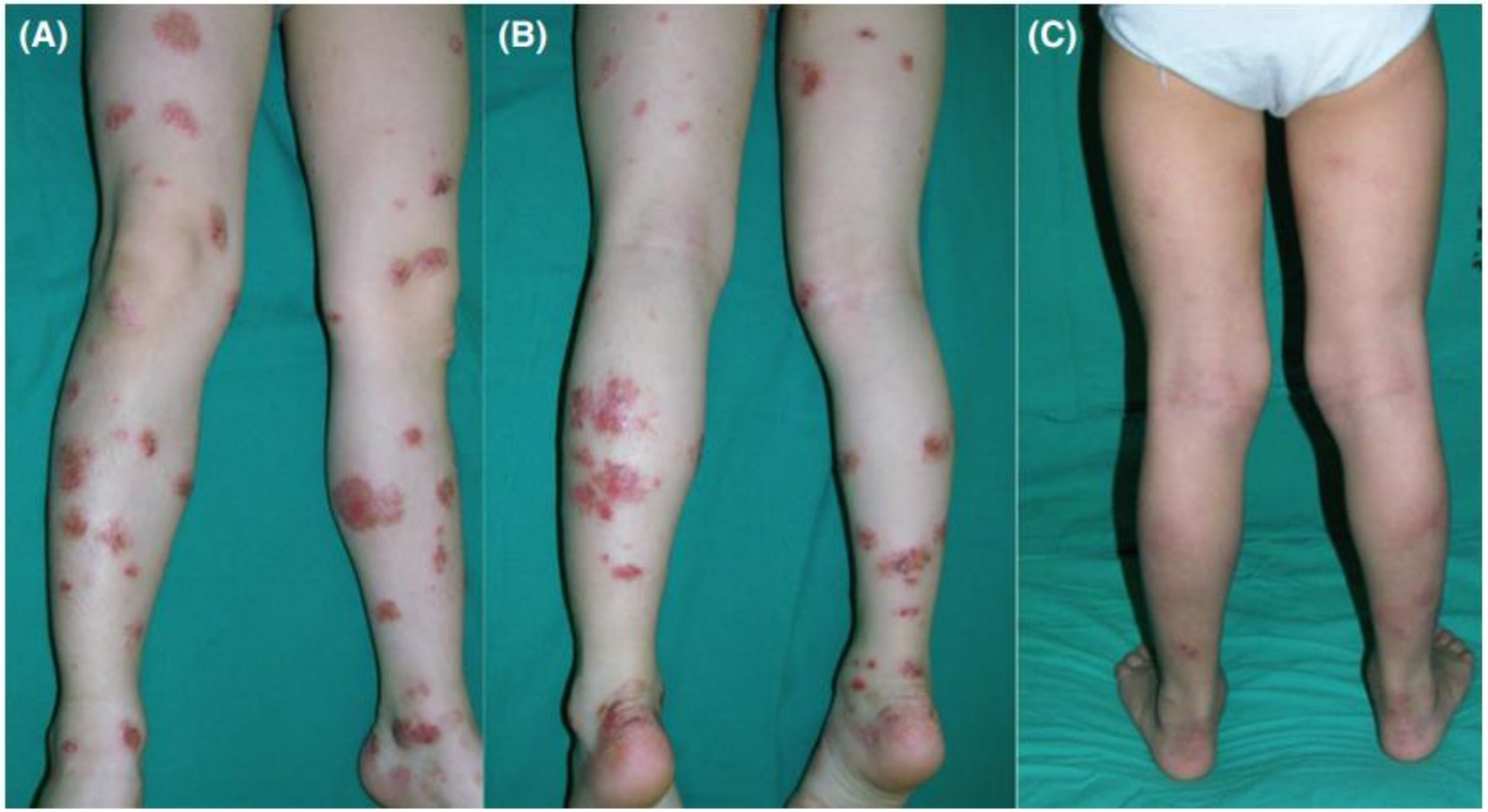
Methods: A retrospective review was undertaken of children with nummular eczema treated with methotrexate between January 2007 and May 2017.

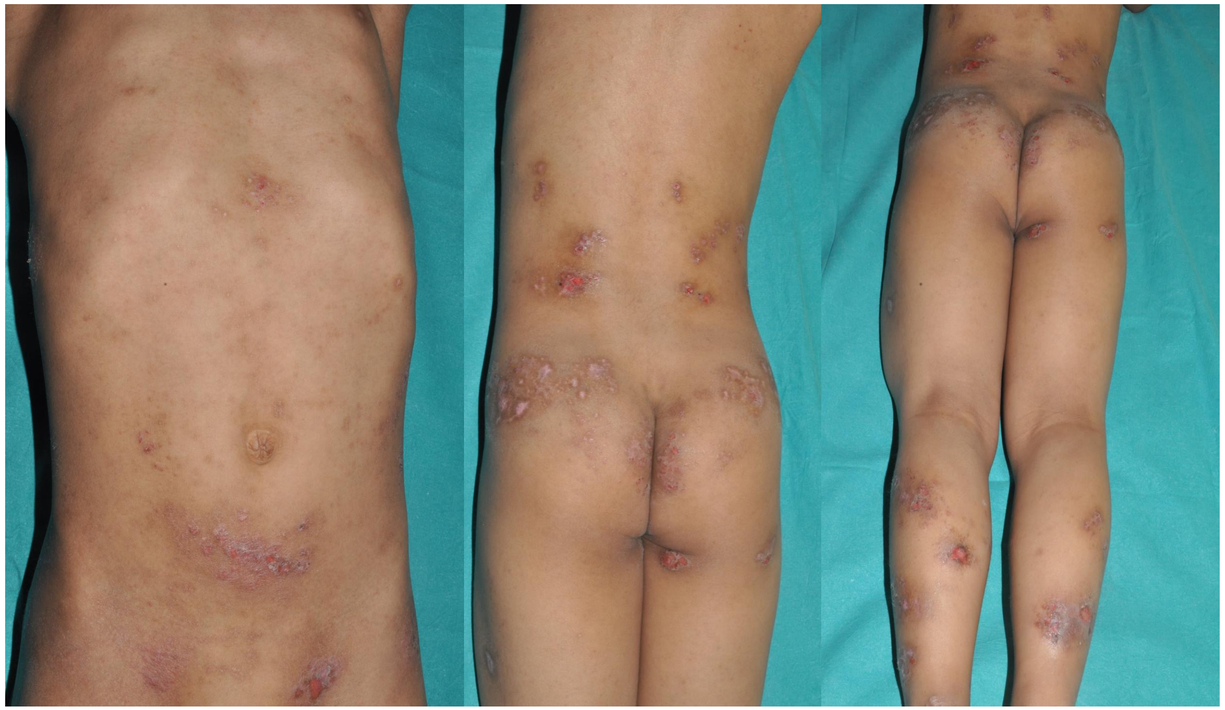
Results: The records of 28 patients (24 male, 4 female) with a mean age at the beginning of treatment of 7.8 ± 1.6 years (95% confidence interval (CI) = 6.1-9.4 years) were reviewed. The median duration of treatment was 12.6 ± 3.3 months (95% CI = 9.2-16 months), and 14 patients were still undergoing methotrexate therapy at the time of last review. Ten patients (35.7%) had complete or almost complete clearance of eczema (> 90% improvement), 13 (46.4%) had marked improvement (50%-89%), four had mild improvement (< 50%), and one failed methotrexate therapy. Gastrointestinal intolerance (21.4%) and a nonsignificant increase in liver enzymes (17.9%) were the most frequent side effects. No serious adverse events were noted.

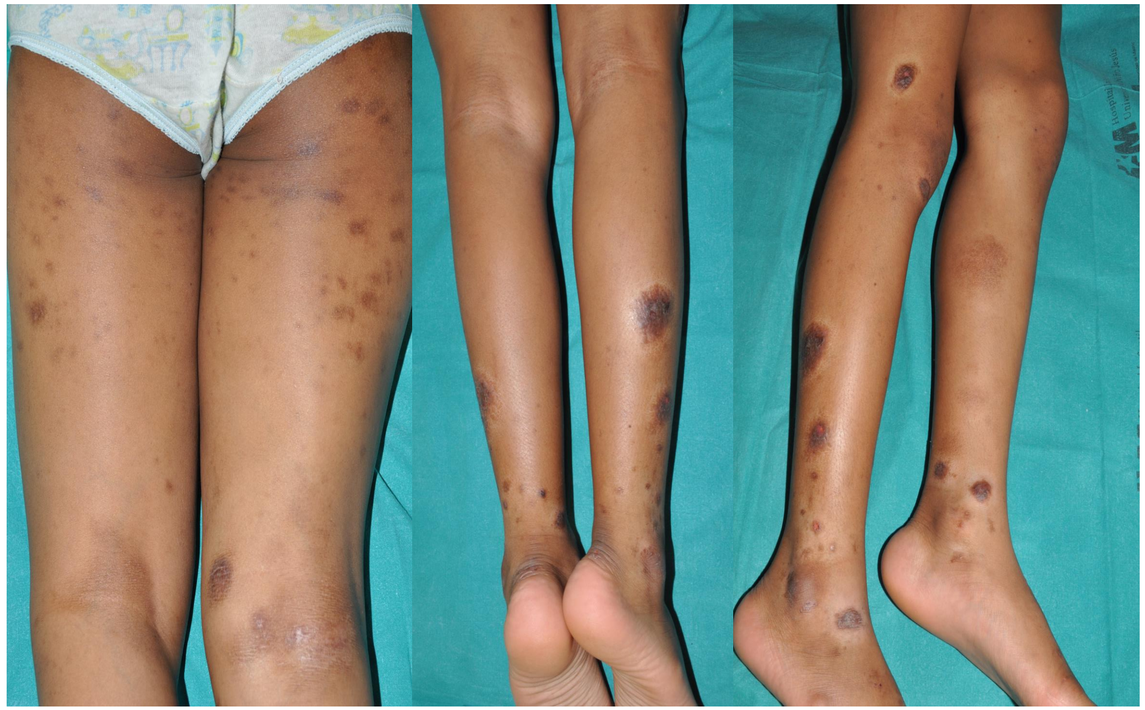
Conclusion: Methotrexate is an effective, well-tolerated treatment in children with moderate to severe nummular eczema that has failed to respond to conventional topical therapy.

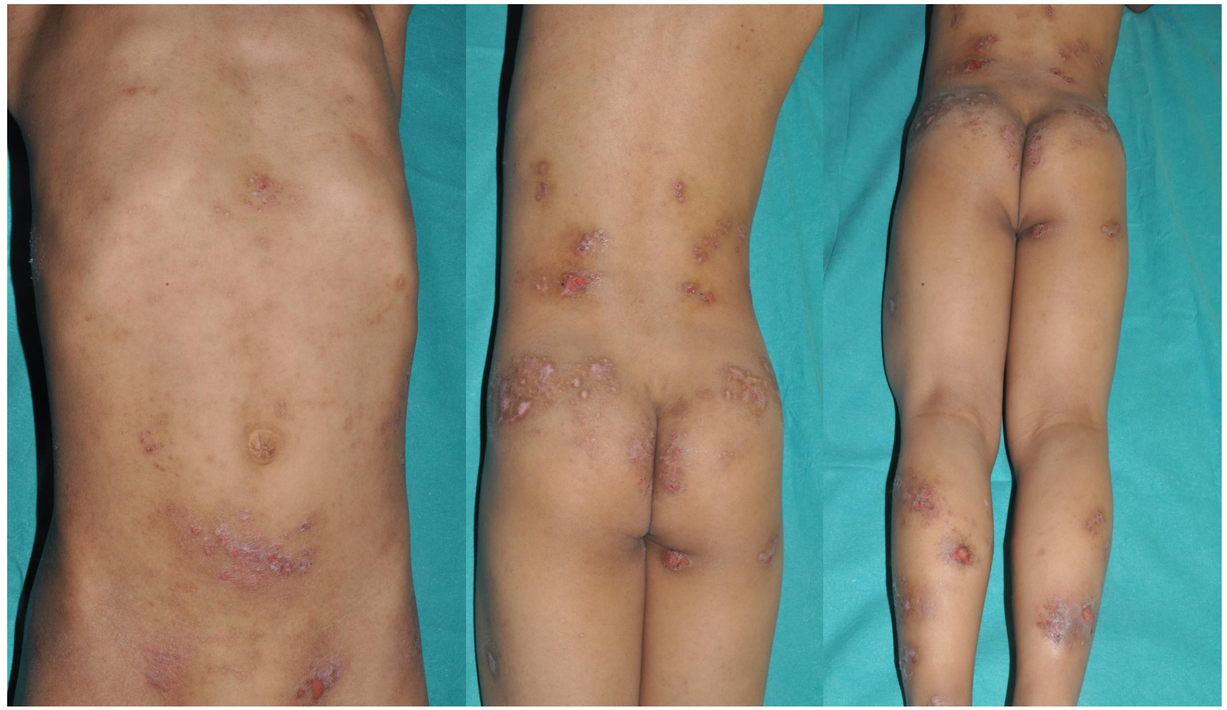
KEYWORDS

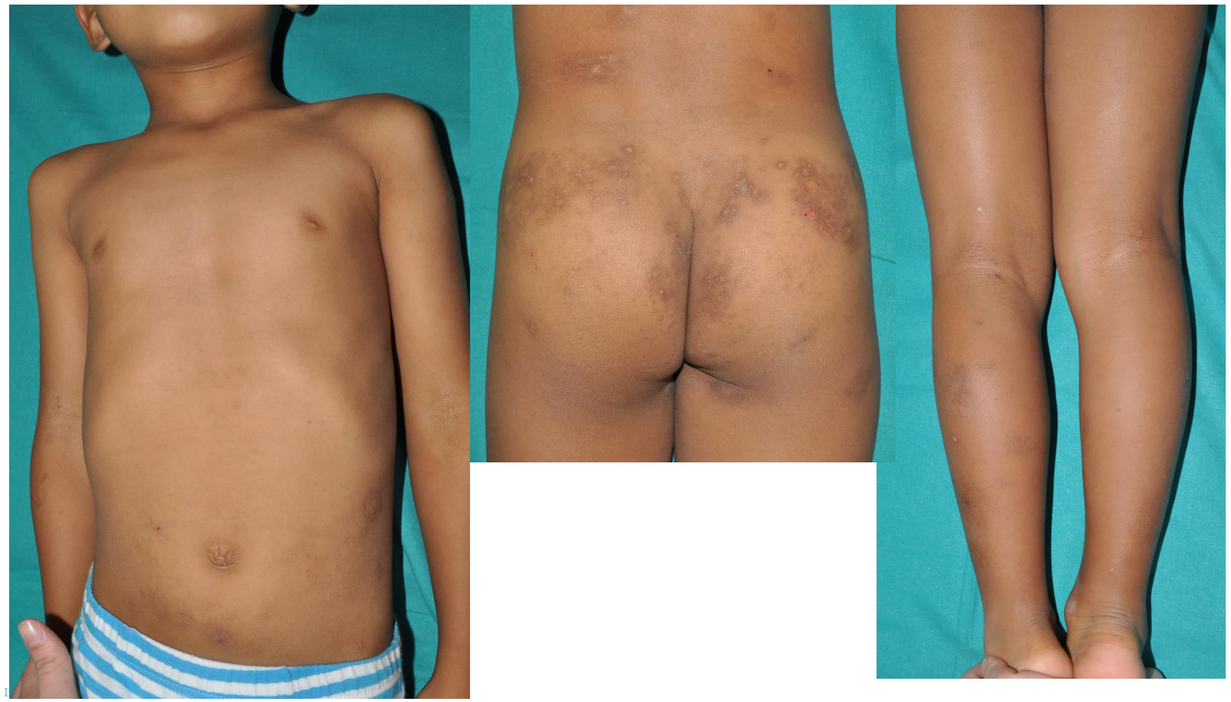
atopic dermatitis, children, immunosuppressant treatment, methotrexate, nummular eczema

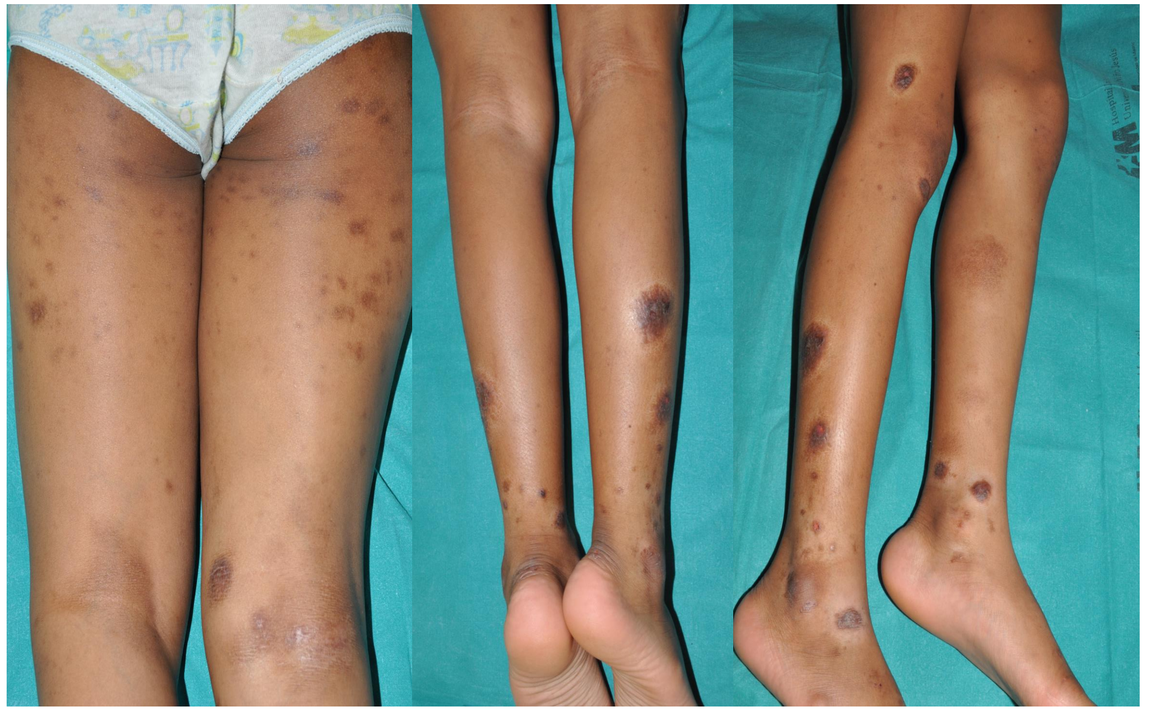


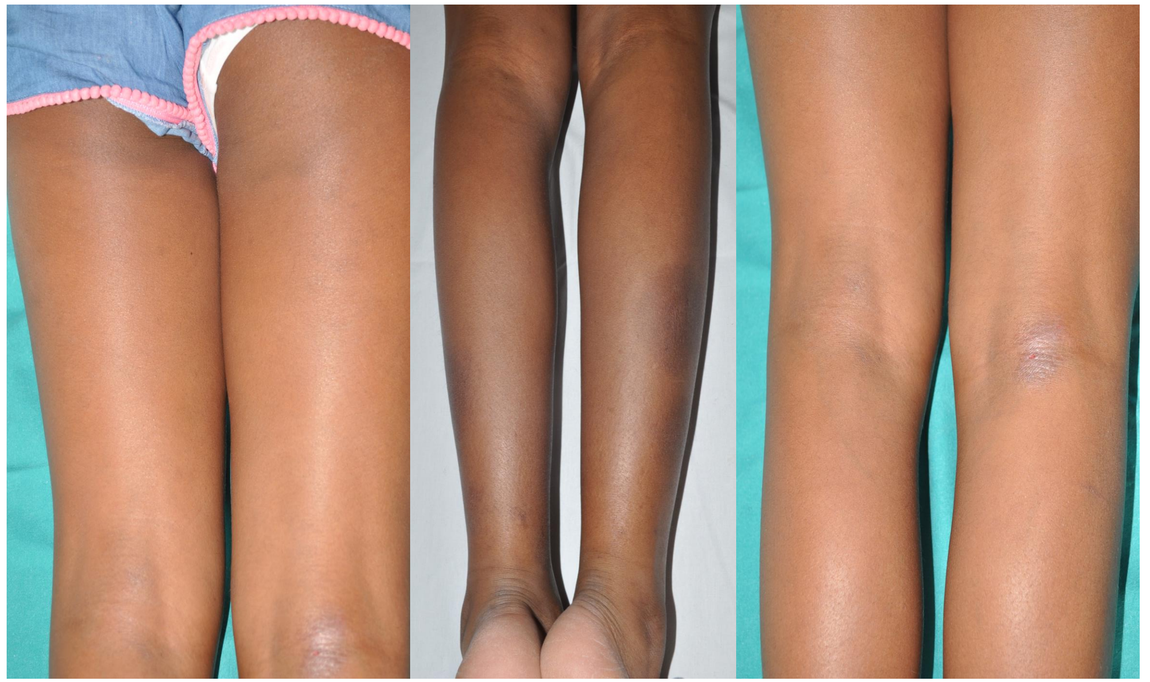


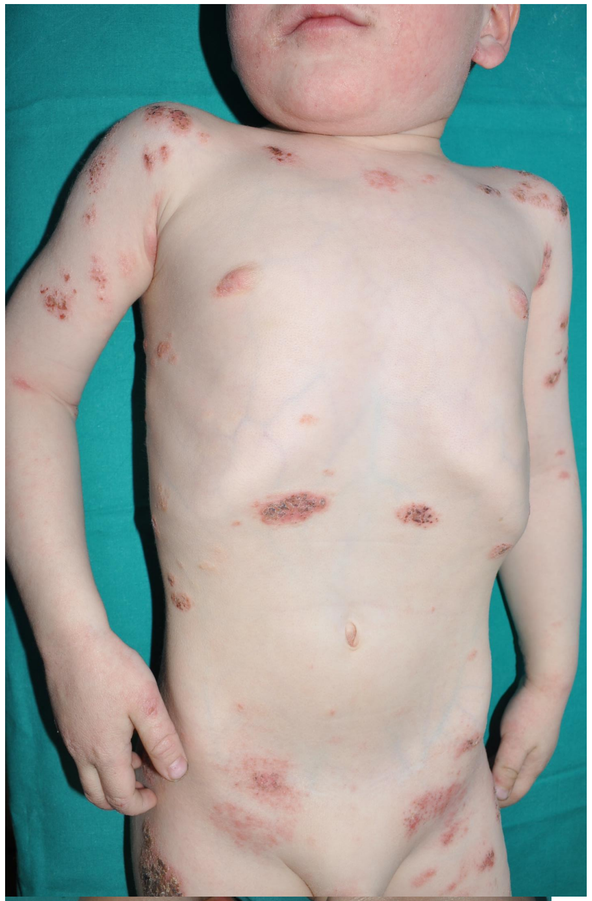


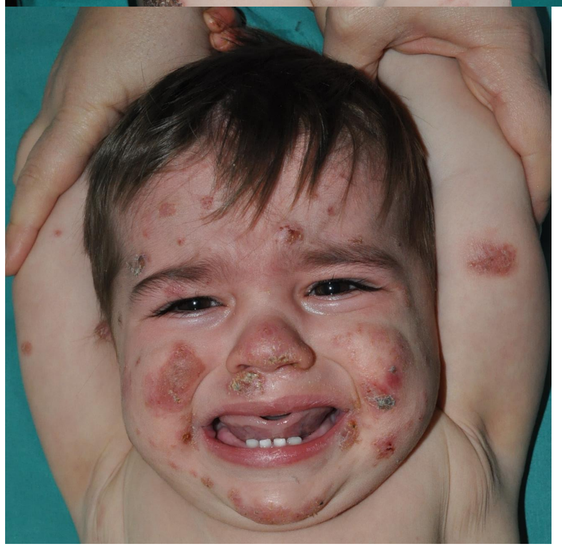


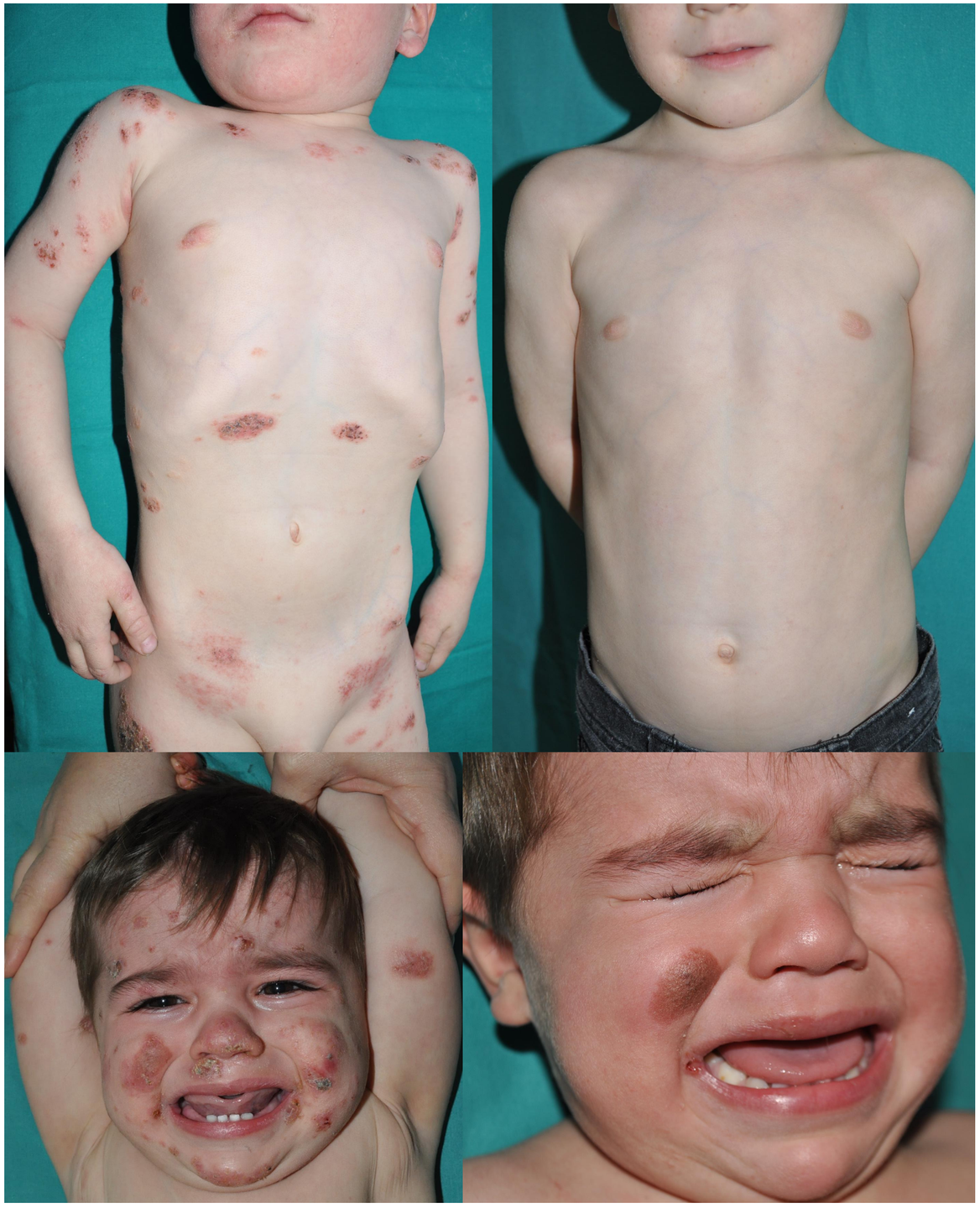


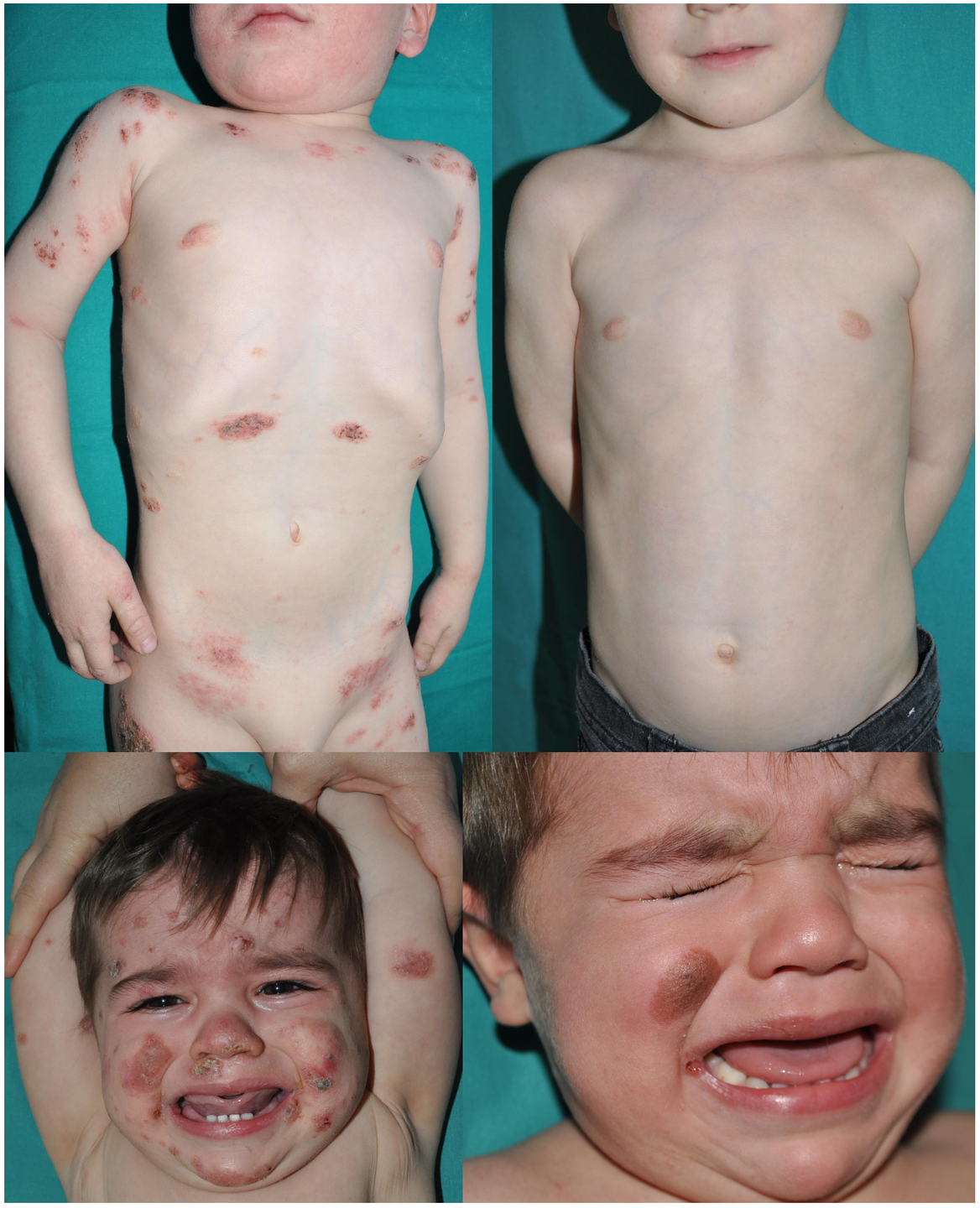












Australasian Journal of Dermatology (2010) **51**, 128–130 doi: 10.1111/j.1440-0960.2010.00634.x

CASE SERIES

Methotrexate is a safe and effective treatment for paediatric discoid (nummular) eczema: A case series of 25 children

Hugh Roberts and David Orchard

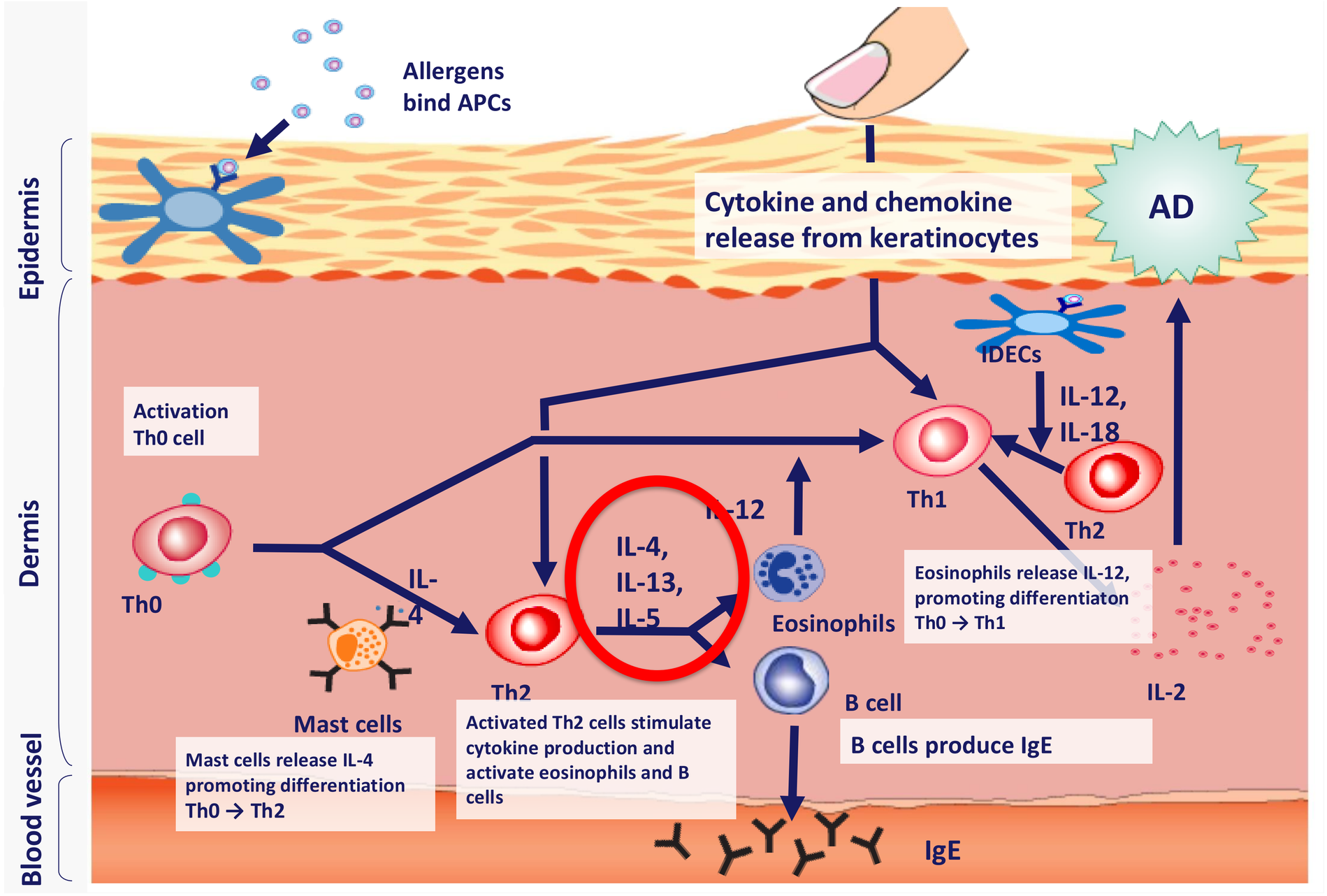
Royal Children's Hospital, Parkville, Melbourne, Victoria, Australia

Table 1 Prior treatment modalities

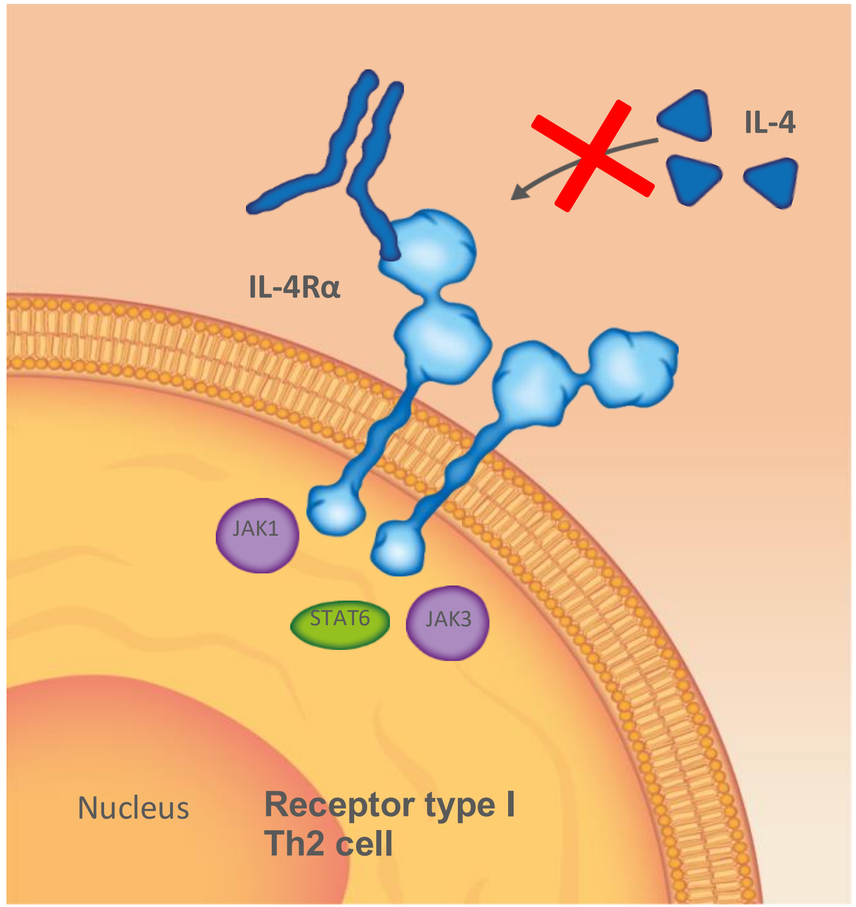
Modality	Number of patients (%)
Topical corticosteroids	25 (100)
Oral antibiotics	25 (100)
Systemic corticosteroids	23 (92)
Wet dressings	20 (80)
Hospital admission	4 (16)
Phototherapy	3 (12)
Cyclosporin	6 (24)
Azathioprine	1 (4)

	Number of patients (%)	Duration of treatment (mean)
Clear	16 (64)	10.5 months
Almost clear	3 (12)	12 months
Ongoing	3 (12)	25 months
Failed†	1 (4)	3 weeks
Lost to follow up	2 (8)	Unknown

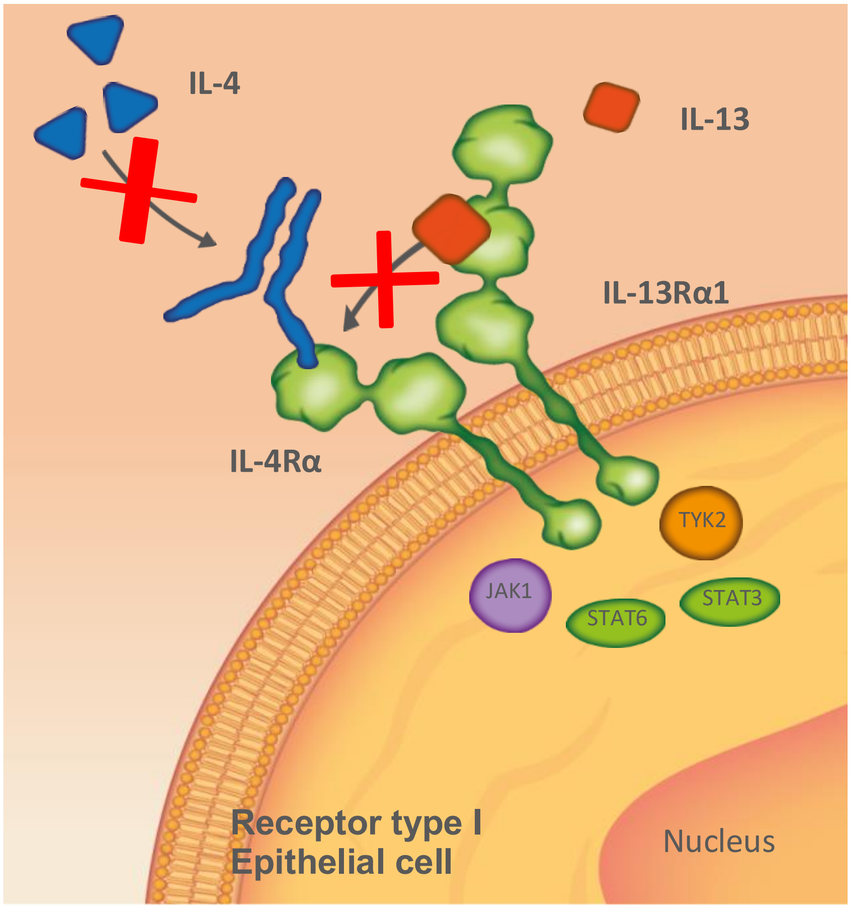
Dupilumab



Dupilumab – Mechanism of action



Expressed in: B cells, T cells, monocytes, eosinophils, fibroblasts



Expressed in: epithelial cells, smooth muscle cellsd, fibroblasts, monocytes, activated B cells

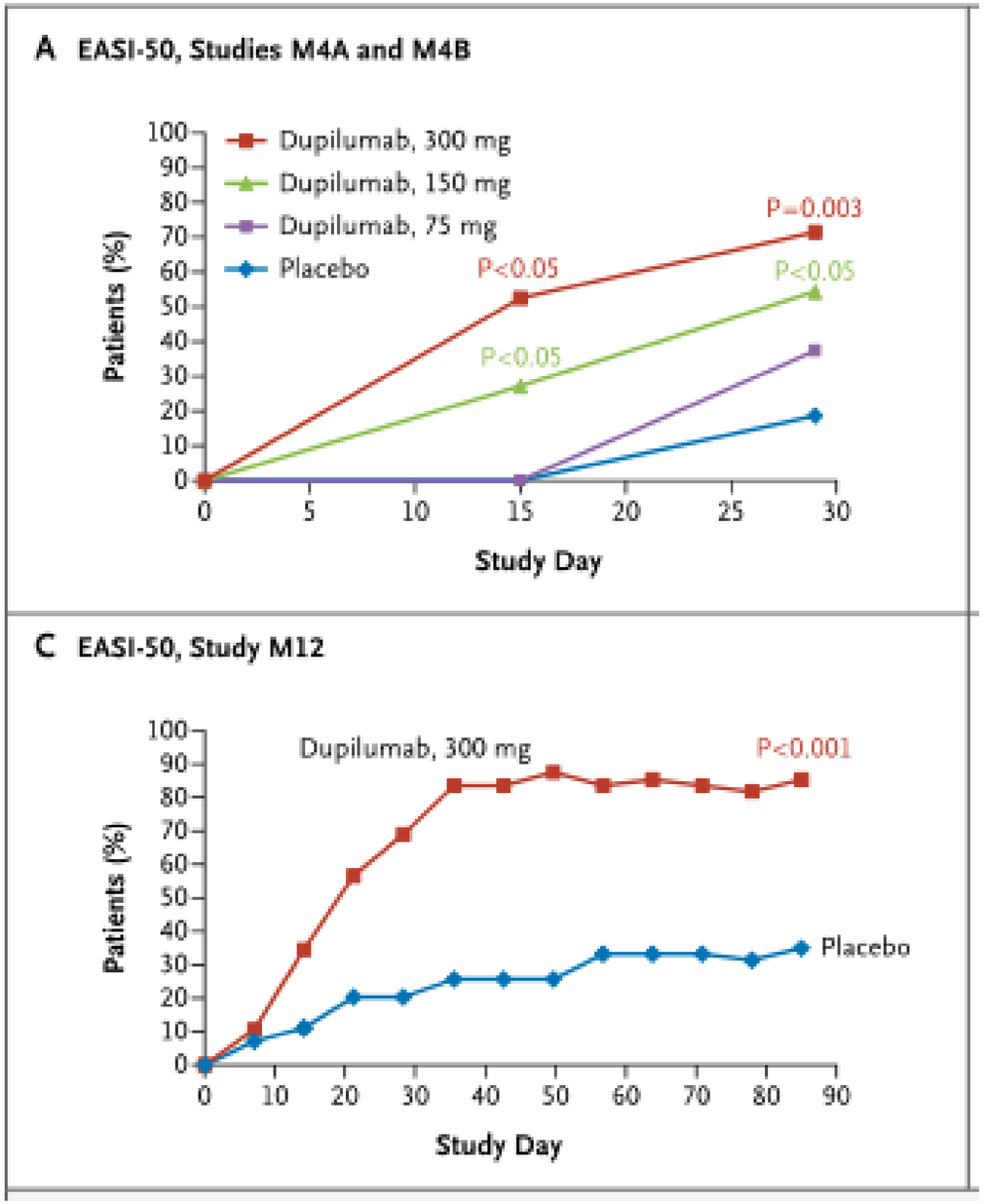
Dupilumab – Efficacy

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

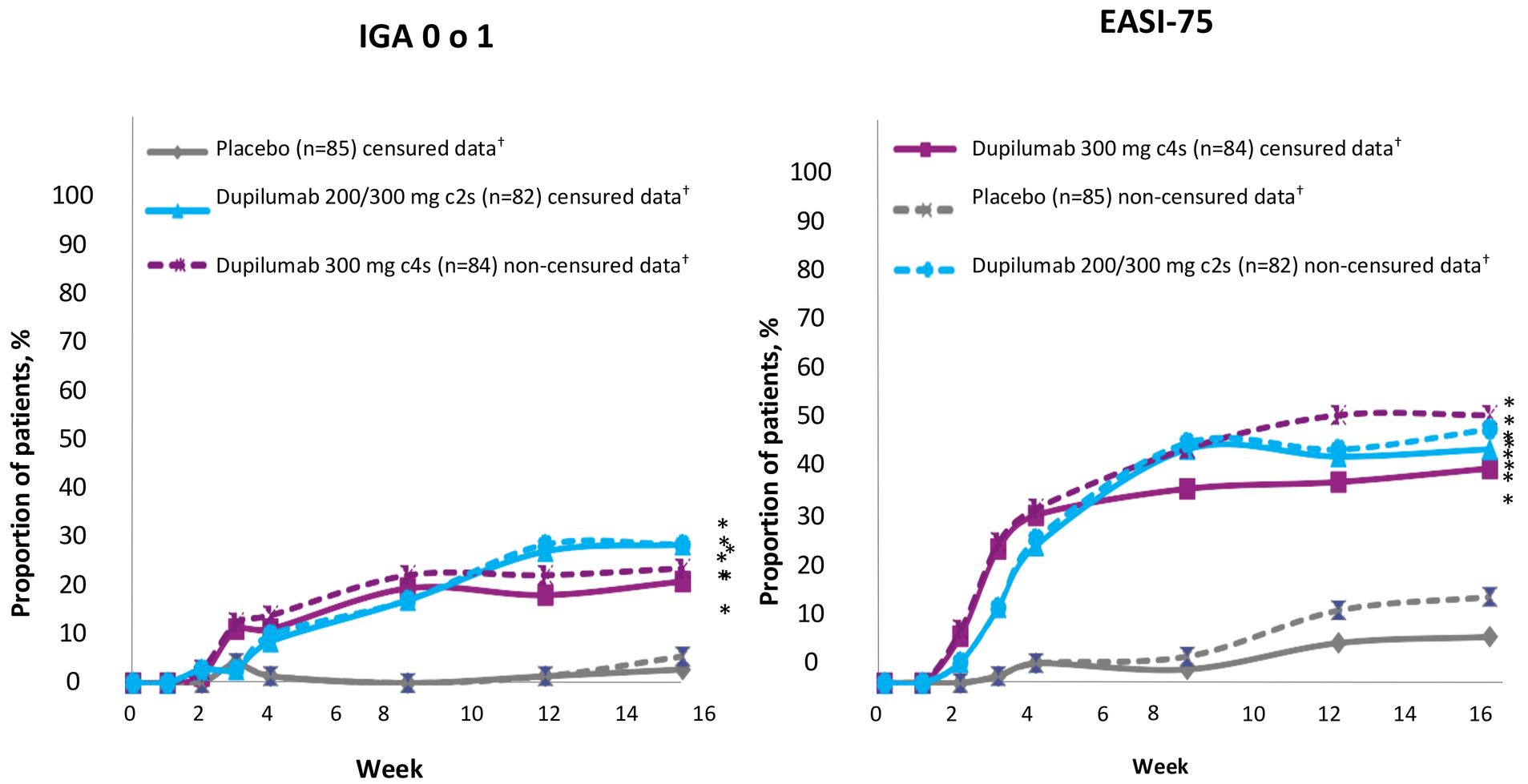
Dupilumab Treatment in Adults with Moderate-to-Severe Atopic Dermatitis

Lisa A. Beck, M.D., Diamant Thaçi, M.D., Jennifer D. Hamilton, Ph.D., Neil M. Graham, M.D., Thomas Bieber, M.D., Ph.D., M.D.R.A., Ross Rocklin, M.D., Jeffrey E. Ming, M.D., Ph.D., Haobo Ren, Ph.D., Richard Kao, Dr.P.H., Eric Simpson, M.D., Marius Ardeleanu, M.D., Steven P. Weinstein, M.D., Ph.D., Gianluca Pirozzi, M.D., Ph.D., Emma Guttman-Yassky, M.D., Ph.D., Mayte Suárez-Fariñas, Ph.D., Melissa D. Hager, M.A., Neil Stahl, Ph.D., George D. Yancopoulos, M.D., Ph.D., and Allen R. Radin, M.D.



Beck et al. N Engl J Med 2014; 371:130-139

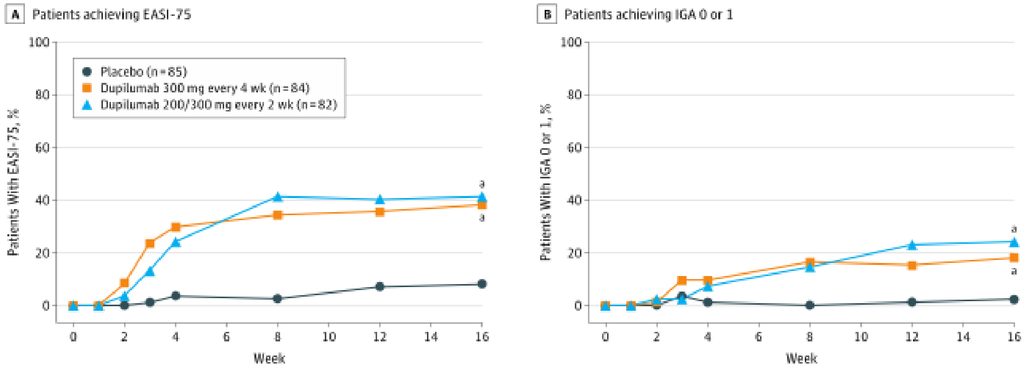
Dupilumab – Efficacy in adolescents

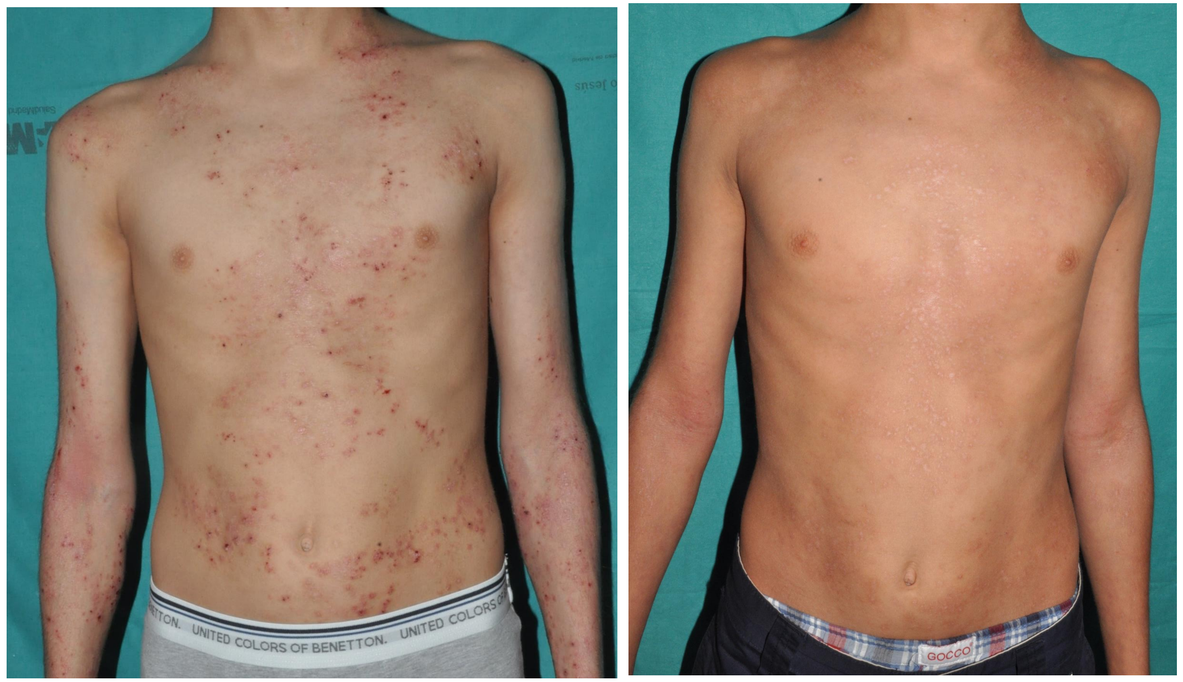


*P < 0,05; **P < 0,001 vs placebo. †Patients considered non-responders after use of rescue treatment. ‡All values observed independently of the use of rescue treatment. IGA, Investigator´s Global Assessment; EASI, Eczema Area and Severity Index; EASI-75, 75% improvement from baseline in EASI index; c4s, every 4 semanas; c2s, every 2 semanas.

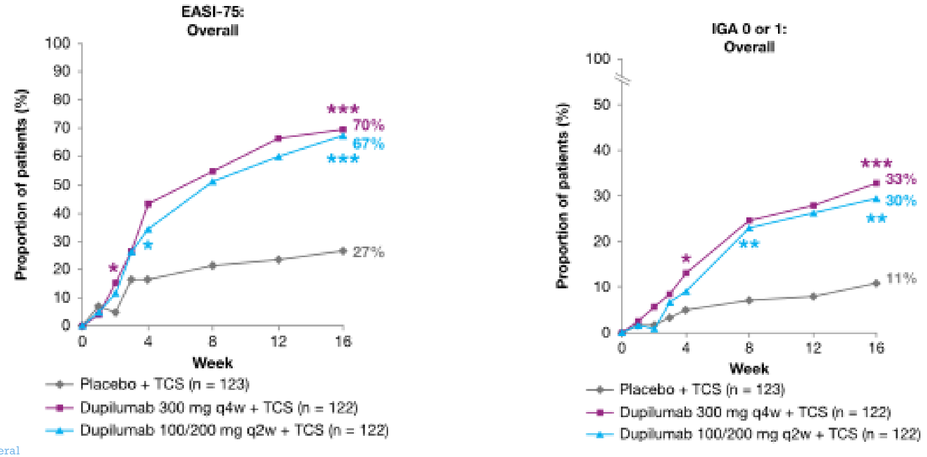
Simpson et al. Dupilumab Efficacy and Safety in Adolescents with Moderate-to-Severe Atopic Dermatitis: Results from a Multicenter, Randomized, PlaceboControlled, Double-Blind, Parallel-Group, Phase 3 Study. EADV 2018

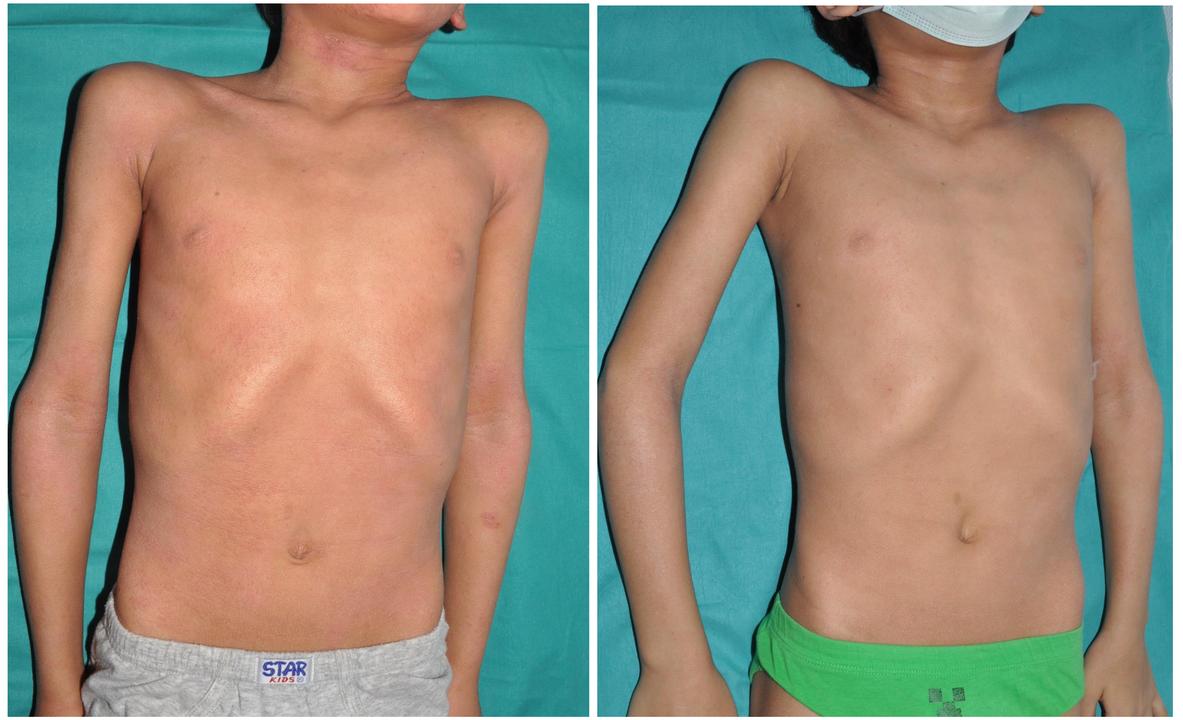
Simpson EL, Paller AS, Siegfried EC, Boguniewicz M, et al . Efficacy and Safety of Dupilumab in Adolescents With Uncontrolled Moderate to Severe Atopic Dermatitis: A Phase 3 Randomized Clinical Trial. JAMA Dermatol. 2020 Jan 1;156(1):44-56. doi: 10.1001/jamadermatol.2019.3336. PMID: 31693077; PMCID: PMC6865265.

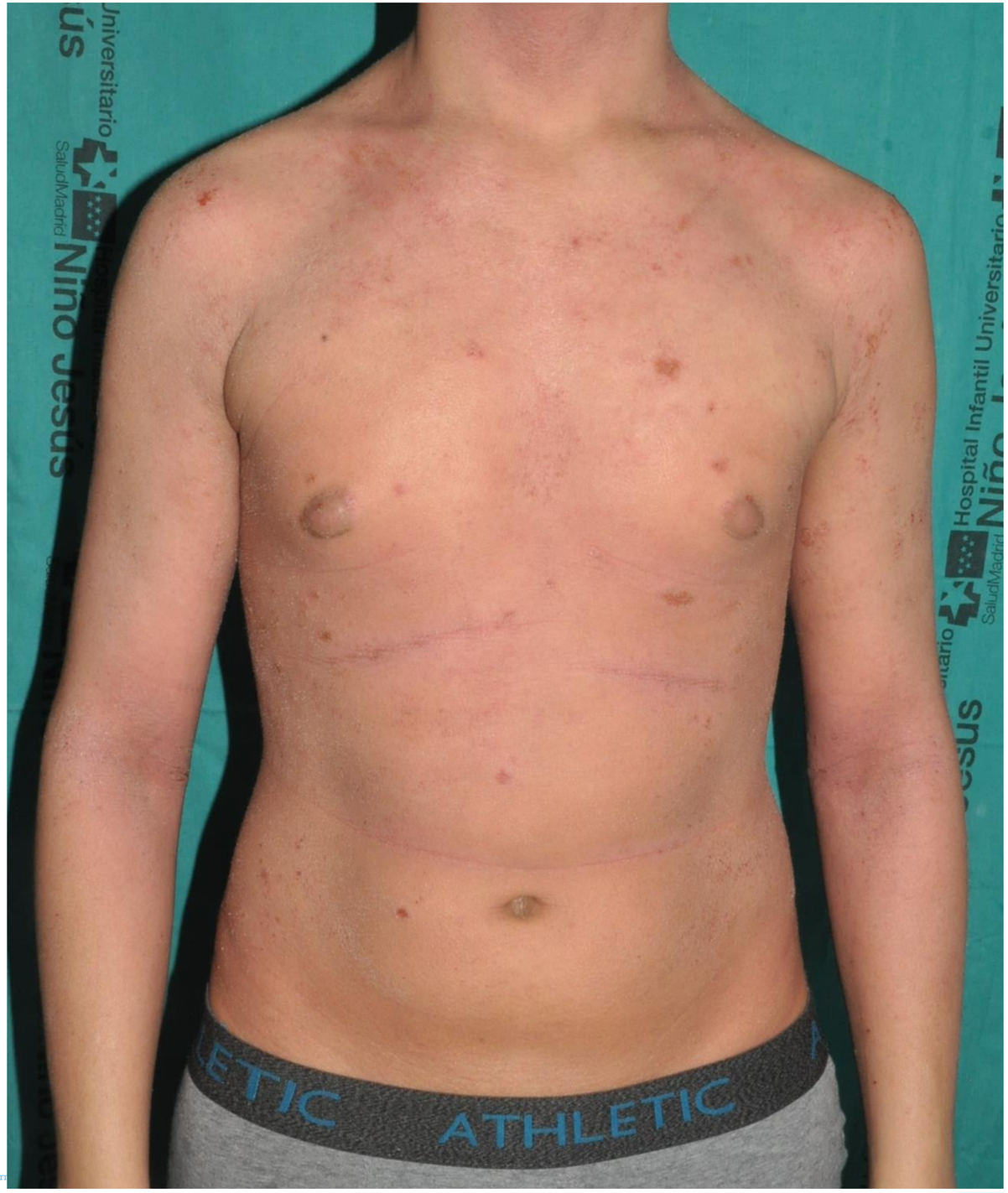




Paller AS, Siegfried EC, Thaçi D, et al . Efficacy and safety of dupilumab with concomitant topical corticosteroids in children 6 to 11 years old with severe atopic dermatitis: A randomized, double-blinded, placebo-controlled phase 3 trial. J Am Acad Dermatol. 2020 Nov;83(5):1282-1293. doi: 10.1016/j.jaad.2020.06.054. Epub 2020 Jun 20. Erratum in: J Am Acad Dermatol. 2021 Jan;84(1):230. PMID: 32574587.



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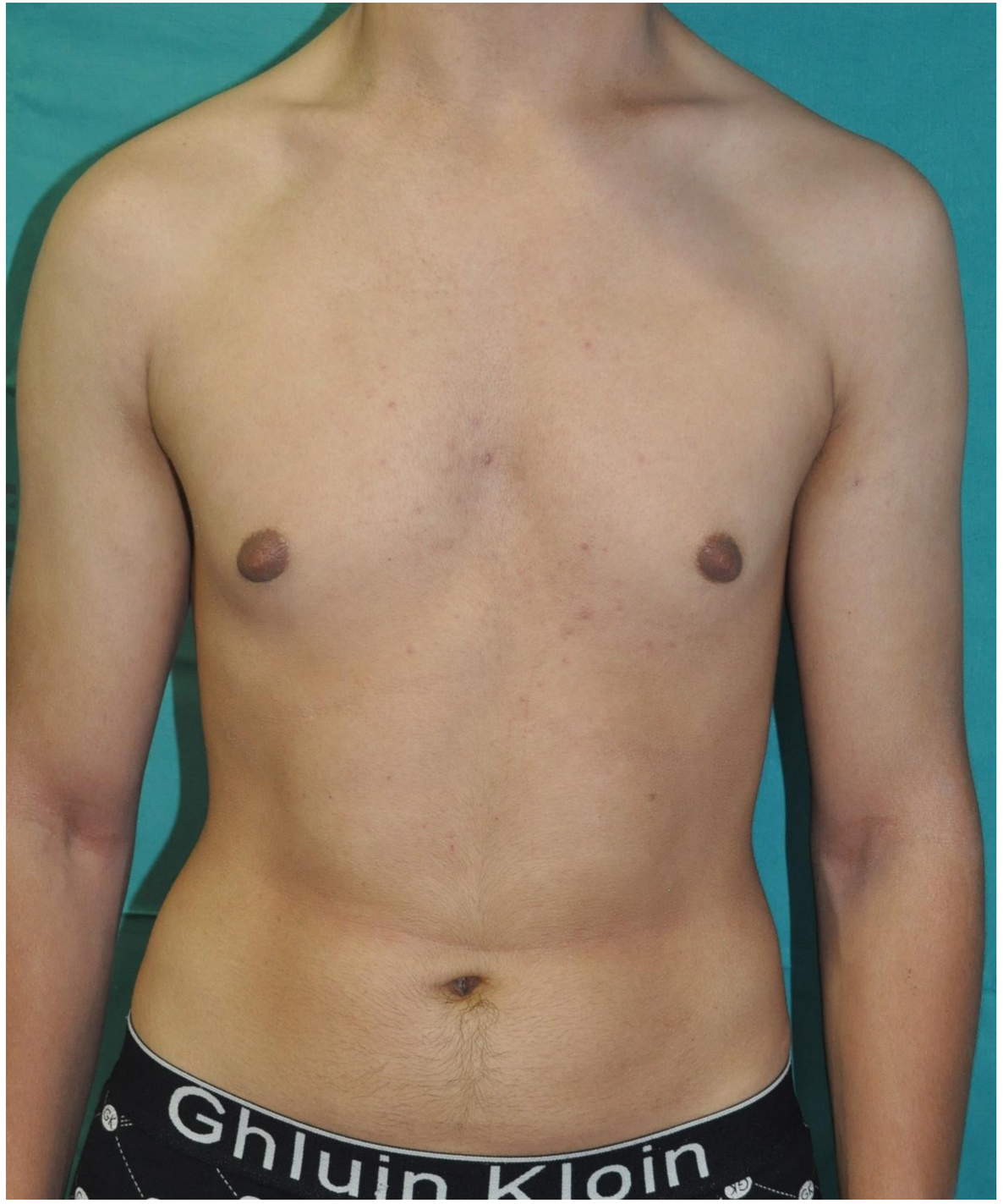
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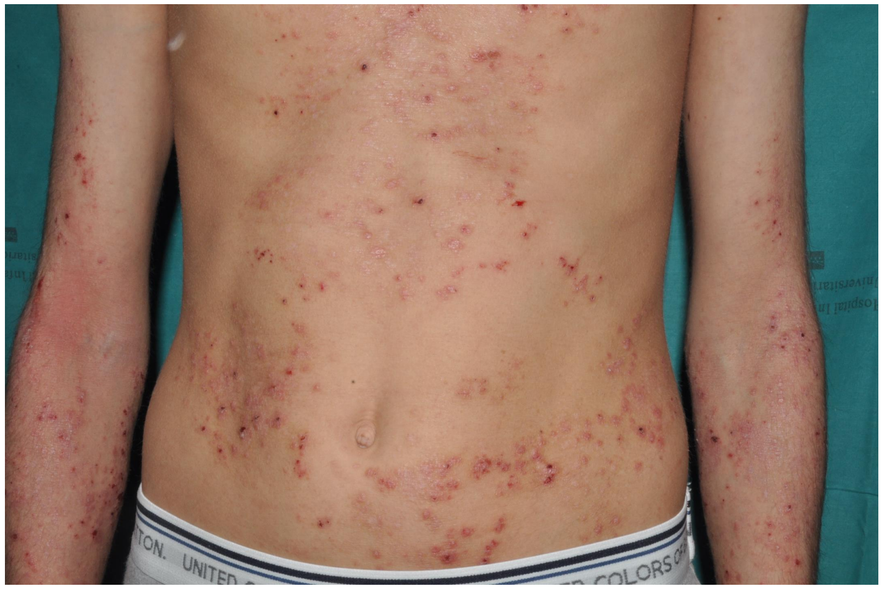

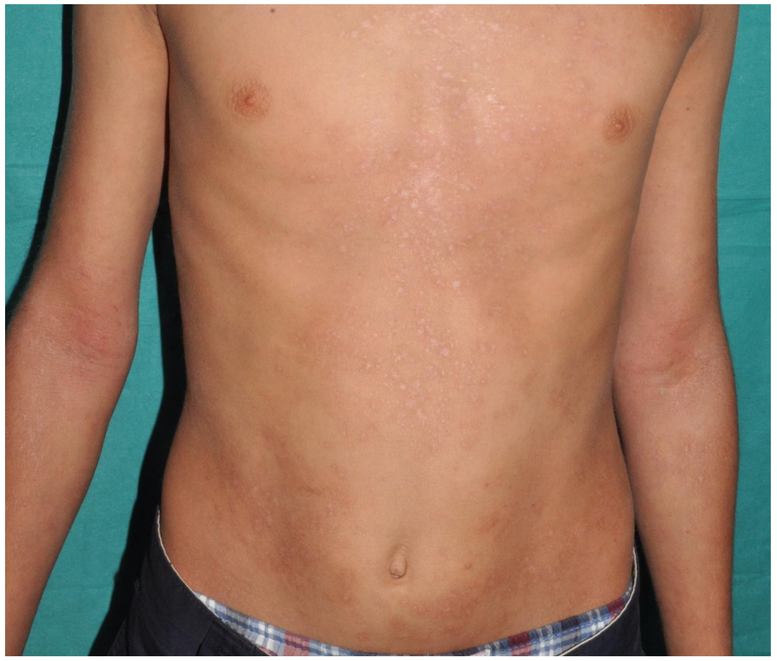

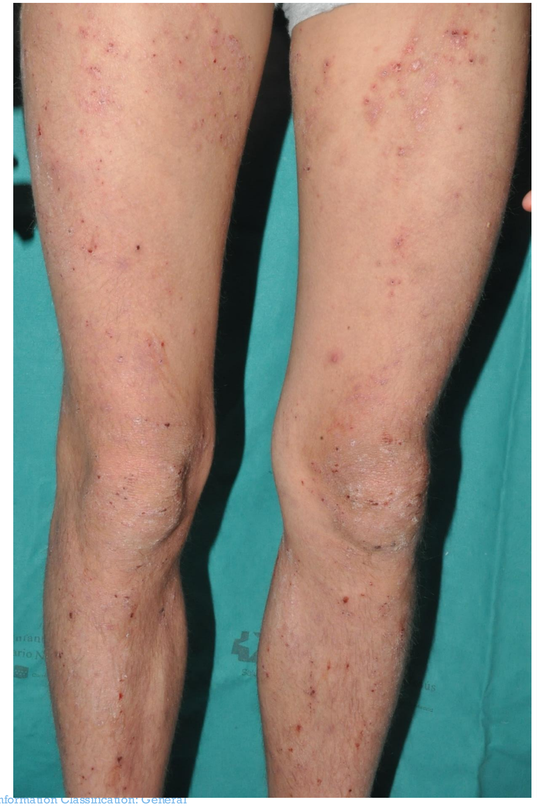

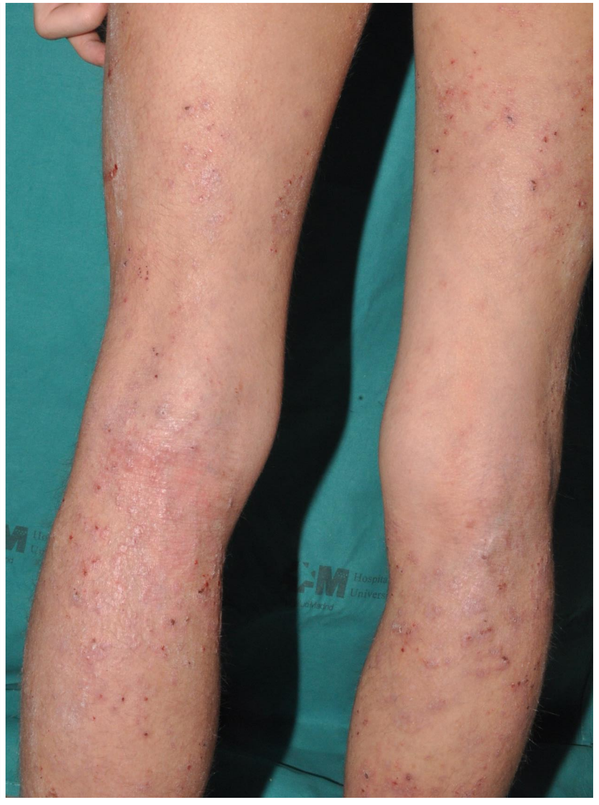

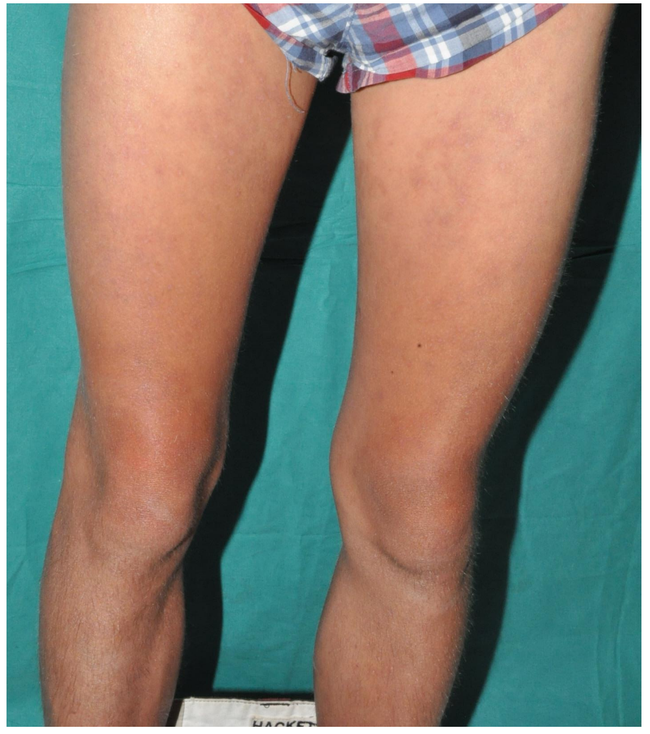

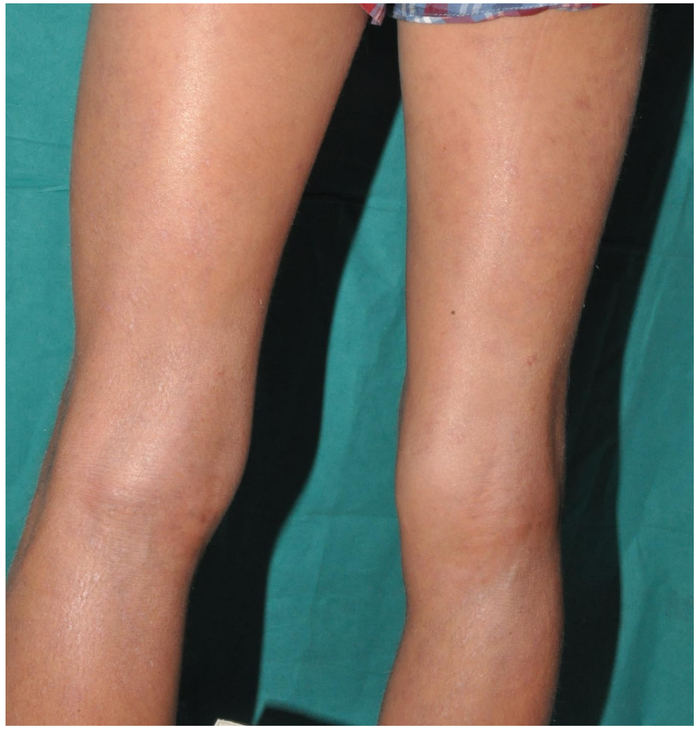

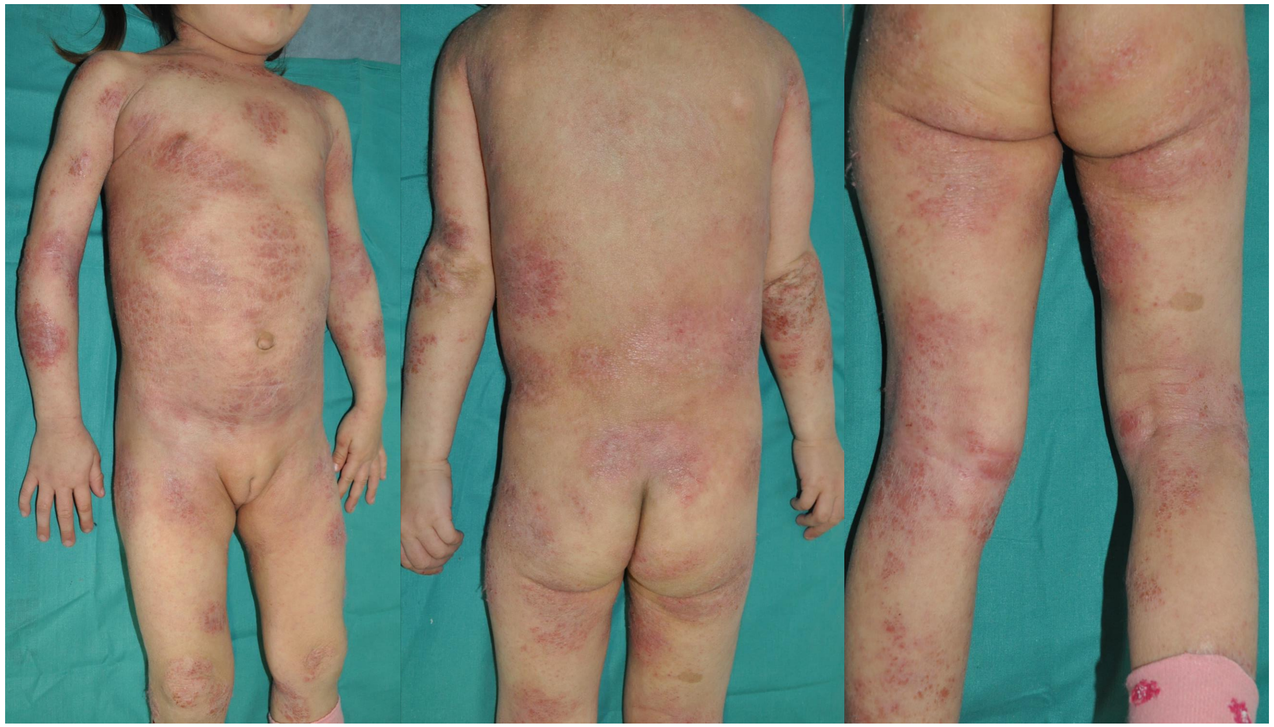

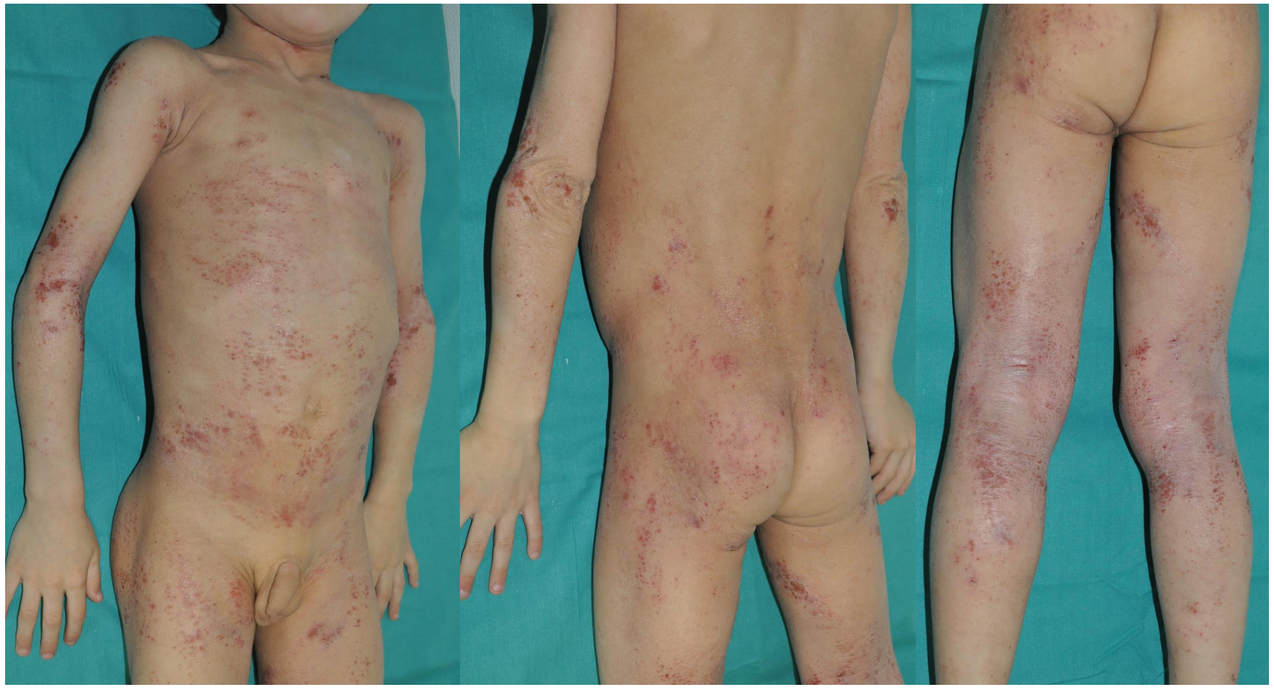

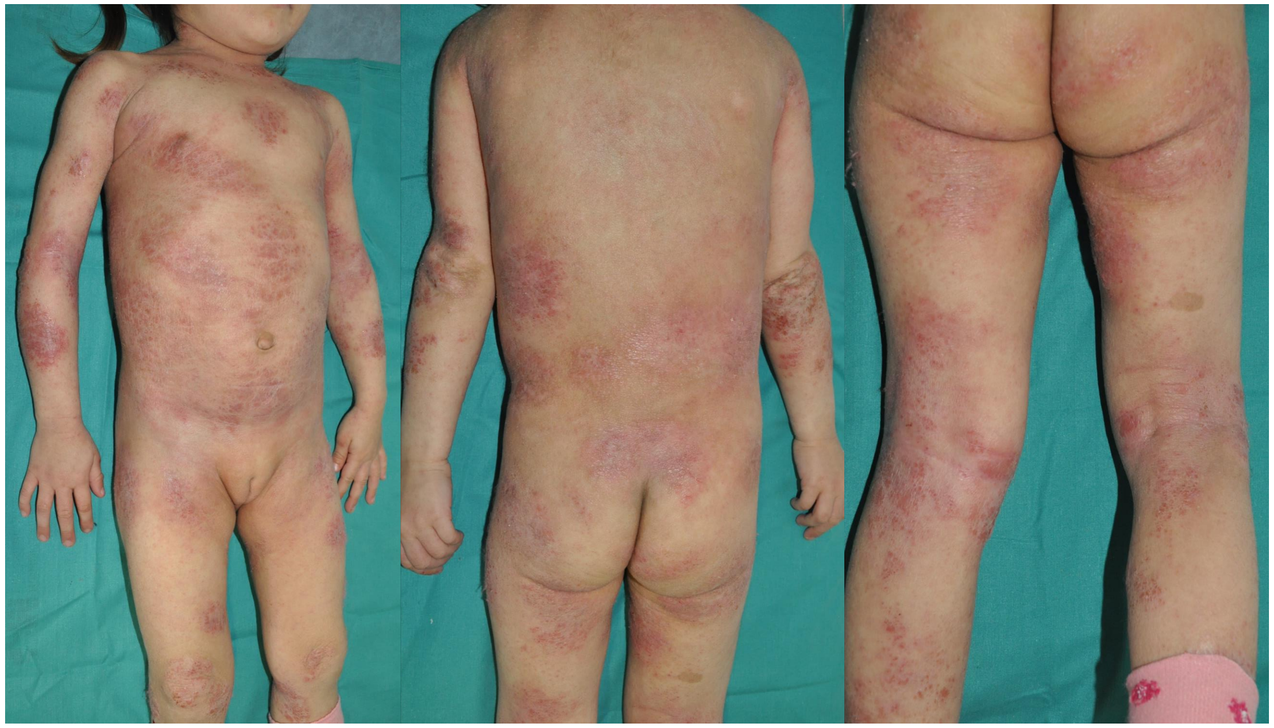

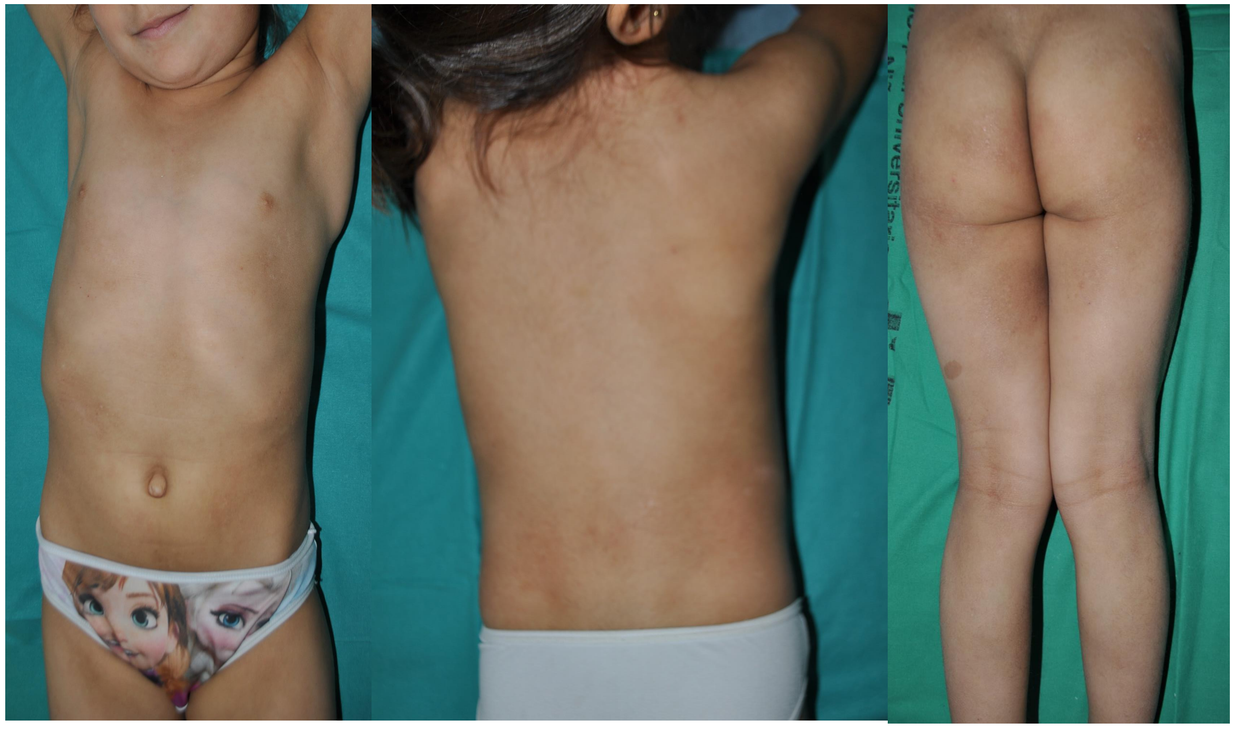

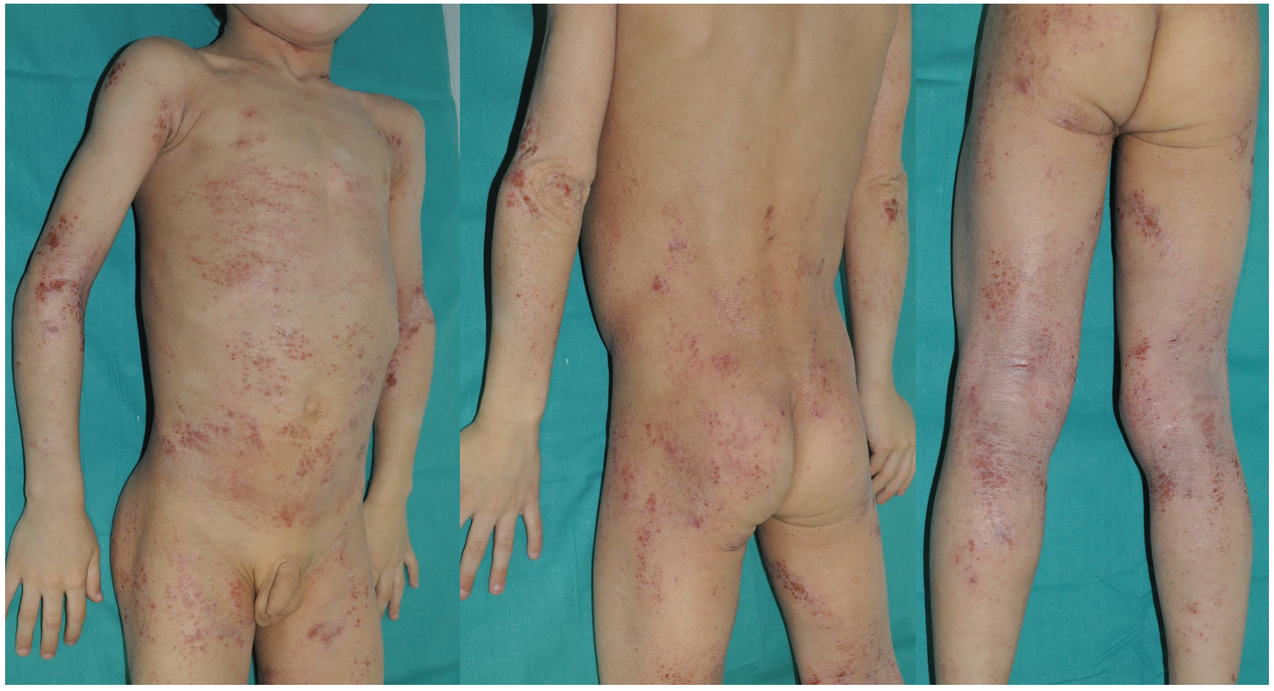

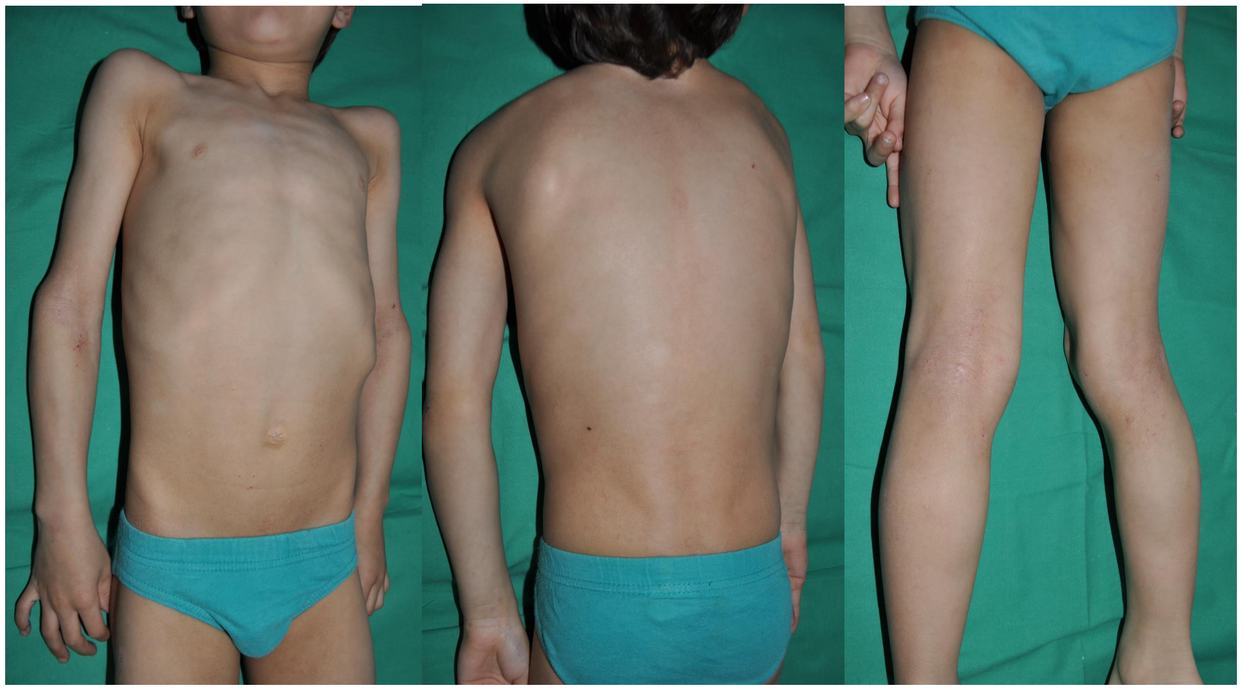

Efficacy and safety of dupilumab in 147 children with AD: 2-year real-world study from a single center

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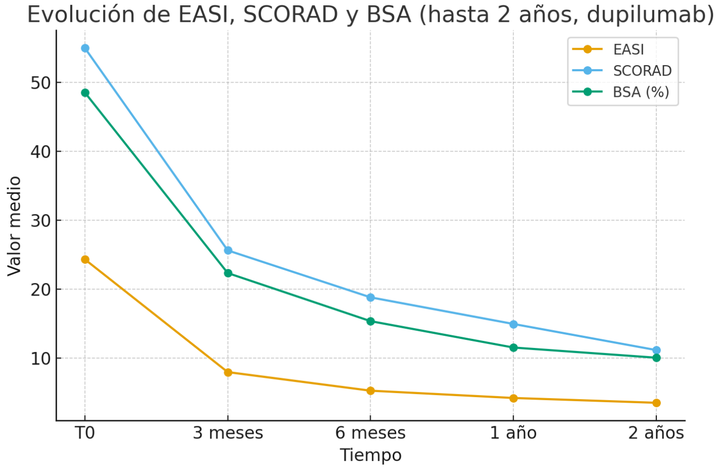
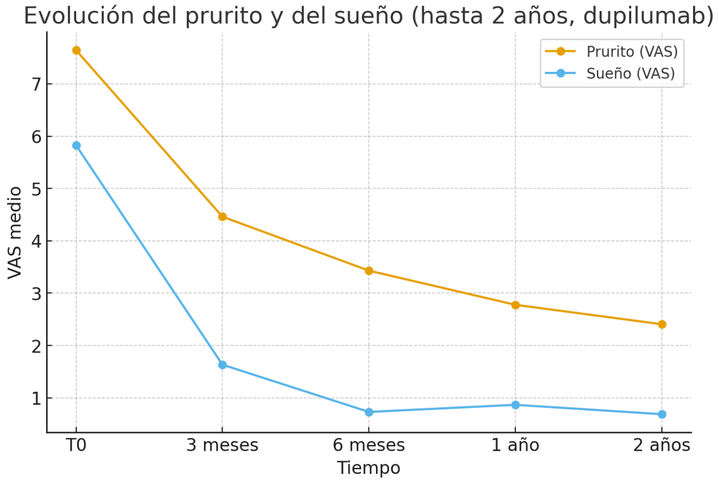
SaludMadrid

Comunidad de Madrid





RESULTS & CONCLUSIONS

- **Quality of life** (pruritus/sleep) improved rapidly and remained stable.
- **Response was consistent across all ages**, with relative superiority in children under 12 years of age.
- **Classic phenotypes** showed the best improvement.
- **Favorable safety profile**, with a low rate of clinically relevant adverse events (11%). The most common were **eosinophilia** (≈ 40 % of adverse events) and **ocular conditions** such as conjunctivitis or ocular pruritus (≈ 35 %).
- **Local injection-site reactions** were less frequent.
- **3% of exposures required treatment discontinuation.**
- **All events were mild or moderate.**

COSTS

- **In our cohort, the mean cumulative cost of dupilumab per patient is approximately €12,000**
- This translates, on an approximate basis, into an **annual cost in the range of €6,000–8,000 per patient per year**, assuming an average treatment duration of around **1.5–2 years**.

Food allergy clinical course in children and adolescents treated with dupilumab for atopic dermatitis

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ABSTRACT

Background: Dupilumab is a monoclonal antibody that inhibits type 2 inflammation through a blockade of interleukin-4 receptor alpha. It is approved for a number of atopic conditions; however, the effect of dupilumab on food allergy has not been fully evaluated.

Objective: To describe the effect of dupilumab use on the clinical course of food allergy in patients receiving dupilumab for comorbid atopic dermatitis.

Methods: This retrospective study reviewed electronic medical records of children with food allergy at a single, tertiary care center receiving dupilumab for the treatment of atopic dermatitis. Food allergy testing, including skin prick test (SPT) and specific IgE (sIgE), and the outcomes of oral food challenges undertaken during routine clinical care were reviewed.

Results: A total of 60 children from 6 months to 18 years of age were included. Linear regression for percent change in measurement by months on dupilumab revealed that sIgE decreased by 0.6% (95% CI −0.8% to −0.4%, $P < .001$) for each additional month of treatment whereas SPT did not differ (0.1% [95% CI −0.6% to 0.7%], $P = .8$). Oral food challenge outcomes in this cohort were similar to previously published cohorts (76% pass rate) undergoing food challenges in a real-world setting irrespective of dupilumab use.

Conclusion: Patients with food allergy receiving dupilumab have greater decreases in sIgE with longer duration of dupilumab treatment whereas SPT seems to be more stable. This suggests that substantial decreases in SPT size over time may be a better correlate of clinical changes in food allergy compared with sIgE in patients with food allergy receiving dupilumab.

Decreased risk of reduced linear growth among children with atopic dermatitis receiving dupilumab: A cohort study

Tai-Li Chen, MD,[a,b] Sheng-Hsiang Ma, MD,[a,b,c] Wei-Fan Ou, MD,[d] Chih-Chiang Chen, MD, PhD,[a,b,e] and Chen-Yi Wu, MD, PhD[a,b,c,f]

Background: Existing studies have shown inconsistent results regarding the association between atopic dermatitis (AD) and linear growth, and the relationship between dupilumab (DUPI) use and height remains unclear.

Objective: This study examines the association between AD and reduced stature in children and evaluates the influence of DUPI on growth outcomes in real-world clinical settings.

Methods: Utilizing the TriNetX US Collaborative Network, we conducted a retrospective cohort study from January 2018 to December 2023 involving children aged <18 years. Children with AD were compared to propensity score–matched non-AD controls to evaluate the risk of falling below the 5th, 25th, and 50th height percentiles. Among children with AD, a target trial emulation framework was applied to compare growth outcomes between those initiating DUPI and those receiving conventional systemic immunomodulators. Cox proportional hazards models, adjusted for relevant confounders, were used to estimate relative risks (RRs) for reduced stature over a 5-year follow-up period.

Results: The study included 745,046 pediatric individuals. Children with AD exhibited a significantly increased risk of reduced height compared to matched controls (<5th percentile: RR 1.15, 95% CI 1.12–1.18; <25th percentile: RR 1.13, 95% CI 1.08–1.21; <50th percentile: RR 1.22, 95% CI 1.20–1.25), with elevated risks particularly evident in males and those aged over 6 years. Sleep disturbance and corticosteroid use emerged as potential effect modifiers. Additionally, among children with AD, treatment with DUPI was associated with a significantly lower risk of falling below the 5th (RR 0.69, 95% CI 0.57–0.84, $P < .001$), 25th (RR 0.70, 95% CI 0.54–0.91, $P < .001$), and 50th (RR 0.74, 95% CI 0.58–0.95, $P < .001$) height percentiles, with the strongest associations observed in males, children over 6 years, and those of body mass index ≥20.

Limitations: The data lack AD severity.

Conclusions: Children with AD are at increased risk of impaired linear growth; however, treatment with DUPI appears to attenuate this risk. These findings highlight the potential growth-preserving benefits of DUPI in the management of pediatric AD and emphasize the importance of routine growth monitoring in this population. (J Am Acad Dermatol 2025;93:1471-80.)

CAPSULE SUMMARY

- Atopic dermatitis in children may be associated with impaired linear growth. Evidence on the impact of dupilumab (DUPI) on growth outcomes is limited.
- This real-world study demonstrates that children with atopic dermatitis have an increased risk of reduced stature compared to those without atopic dermatitis. Treatment with DUPI is associated with a lower risk of growth impairment than conventional systemic immunomodulators, suggesting a possible protective effect of DUPI on linear growth in pediatric patients.

Dupilumab response in children and adolescents with atopic dermatitis across racial and ethnic groups: A retrospective cohort study

Table I. Demographics of pediatric patients with atopic dermatitis on dupilumab

Measure	Item	Count (%)
Sex	Male	116 (49.2%)
	Female	120 (50.8%)
Age	1-5 y	33 (14.0%)
	6-11 y	76 (32.2%)
	12-17 y	127 (53.8%)
Race/ethnicity	White Hispanic	21 (8.9%)
	Non-White Hispanic	52 (22.0%)
	Black Non-Hispanic	30 (12.7%)
	Asian Non-Hispanic	41 (17.4%)
	White Non-Hispanic	92 (39.0%)
Race (generalized)	Non-White	123 (52.1%)
	White	113 (47.9%)

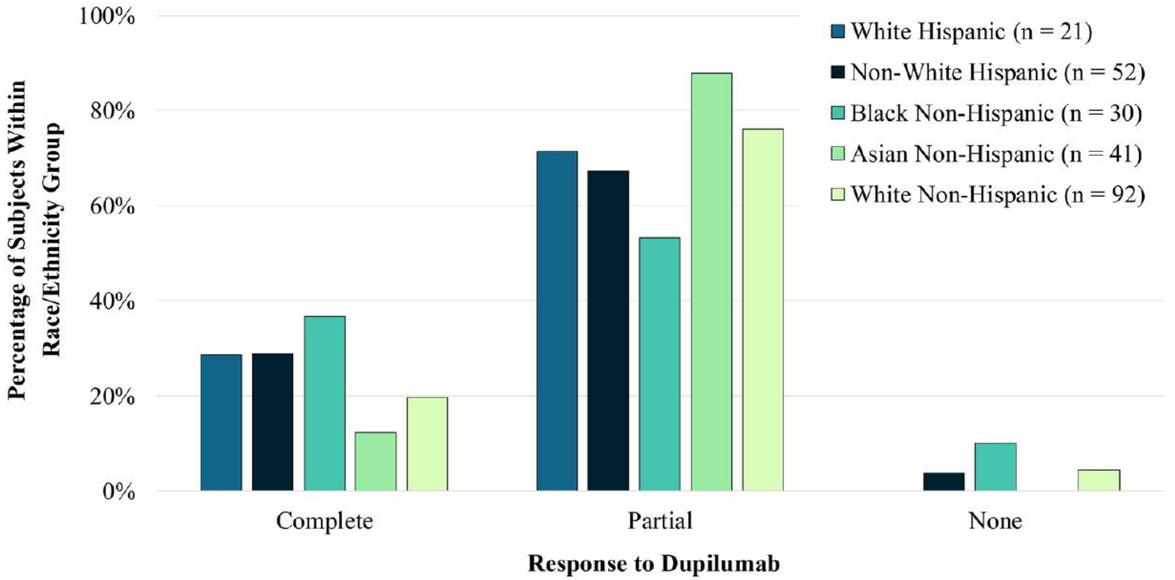


Fig 1. Degree of dupilumab response in atopic dermatitis vs specific race/ethnicity groups.

Our data suggest that race and ethnicity do not affect the degree to which a child or adolescent may respond to dupilumab.

Jared Boetes, BS,[a,b] Sarah Kamsiah Zemlok, BA,[b,c] Kyle Polen, BS,[a] Ether Dharmesh, BS,[a] and JiaDe Yu, MD, MS[b,d]

From the Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania[a]; Department of Dermatology, Massachusetts General Hospital, Boston, Massachusetts[b]; University of Connecticut School of Medicine, Farmington, Connecticut[c]; and Harvard Medical School, Boston, Massachusetts.[d]

Characterizing Dupilumab Facial Redness in Children and Adolescents: A Single-Institution Retrospective Chart Review

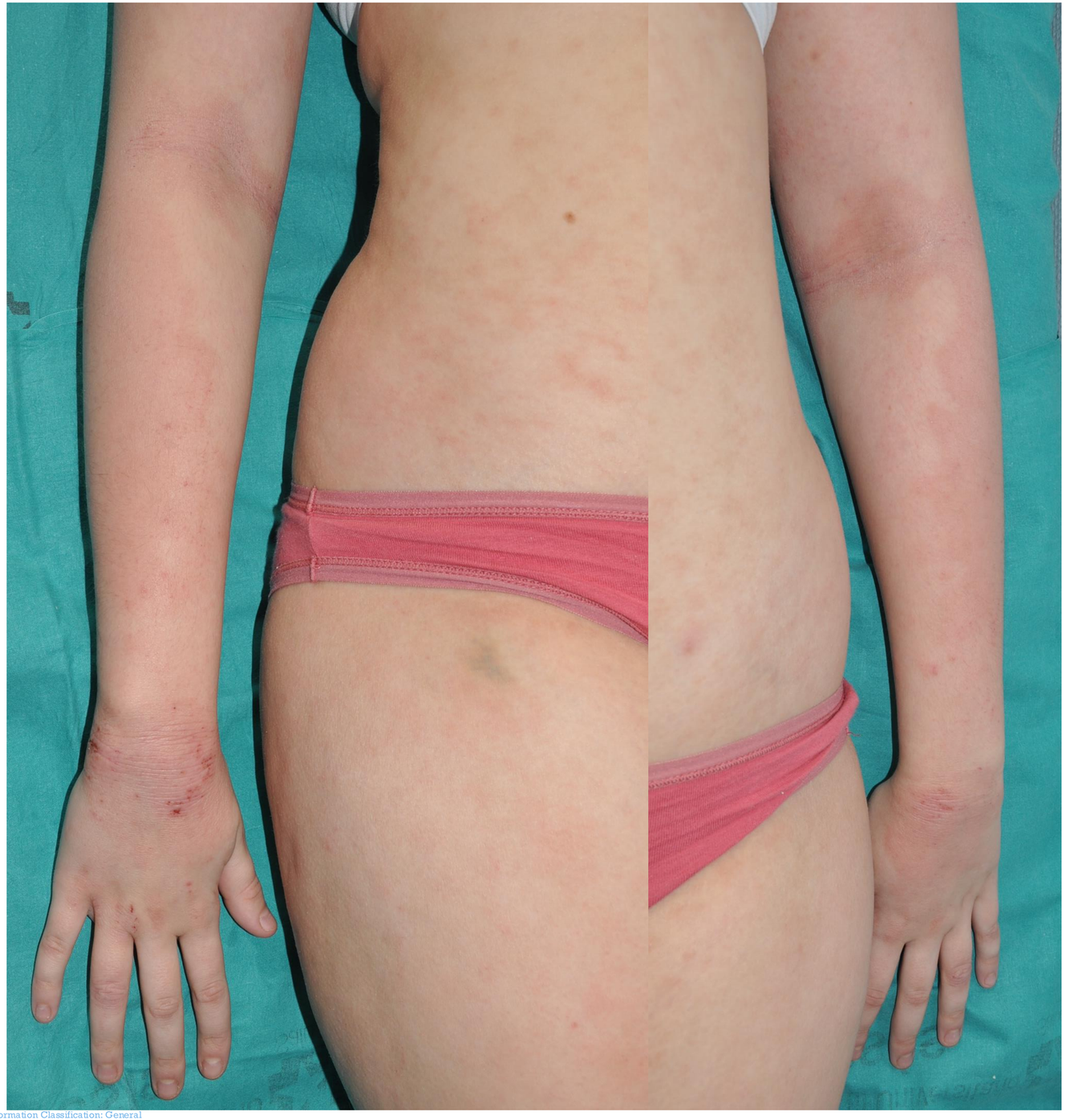
Sonal Muzumdar, Micaella Zubkov, Reid Waldman, MD, Madeline E. DeWane, MD, Rong Wu, PhD, Jane M. Grant-Kels, MD

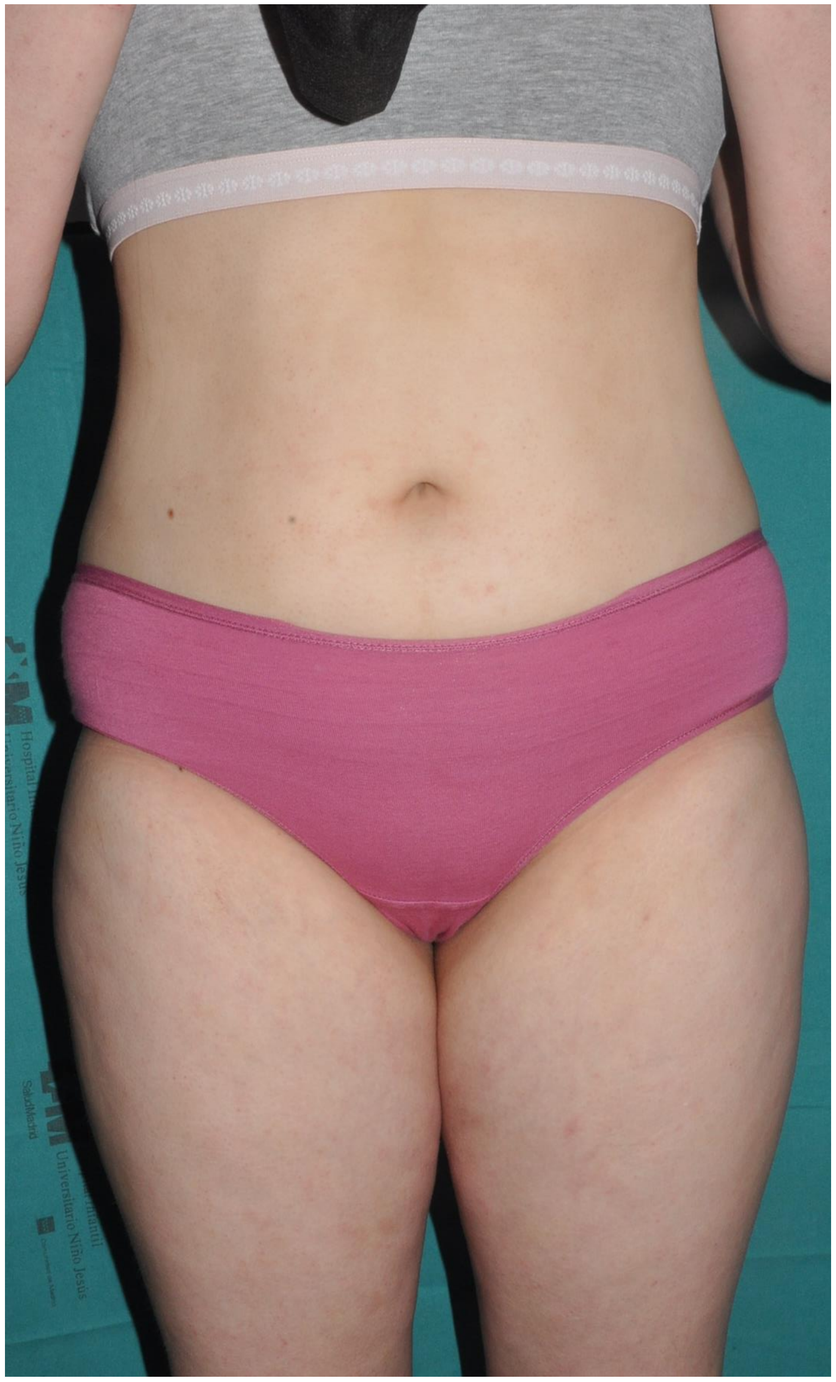
- New-onset, paradoxical flaring of facial dermatitis
- Present in 10 % of patients with Dupilumab
- 7 of 24 (29%) children treated had worsening or new-onset facial dermatitis
- More frequent in postpubertal children
- A seborrheic-like dermatitis (with IL-4 blockade facilitating a Th17 response) ?
- Treatment with 2 % ketoconazole cream ?

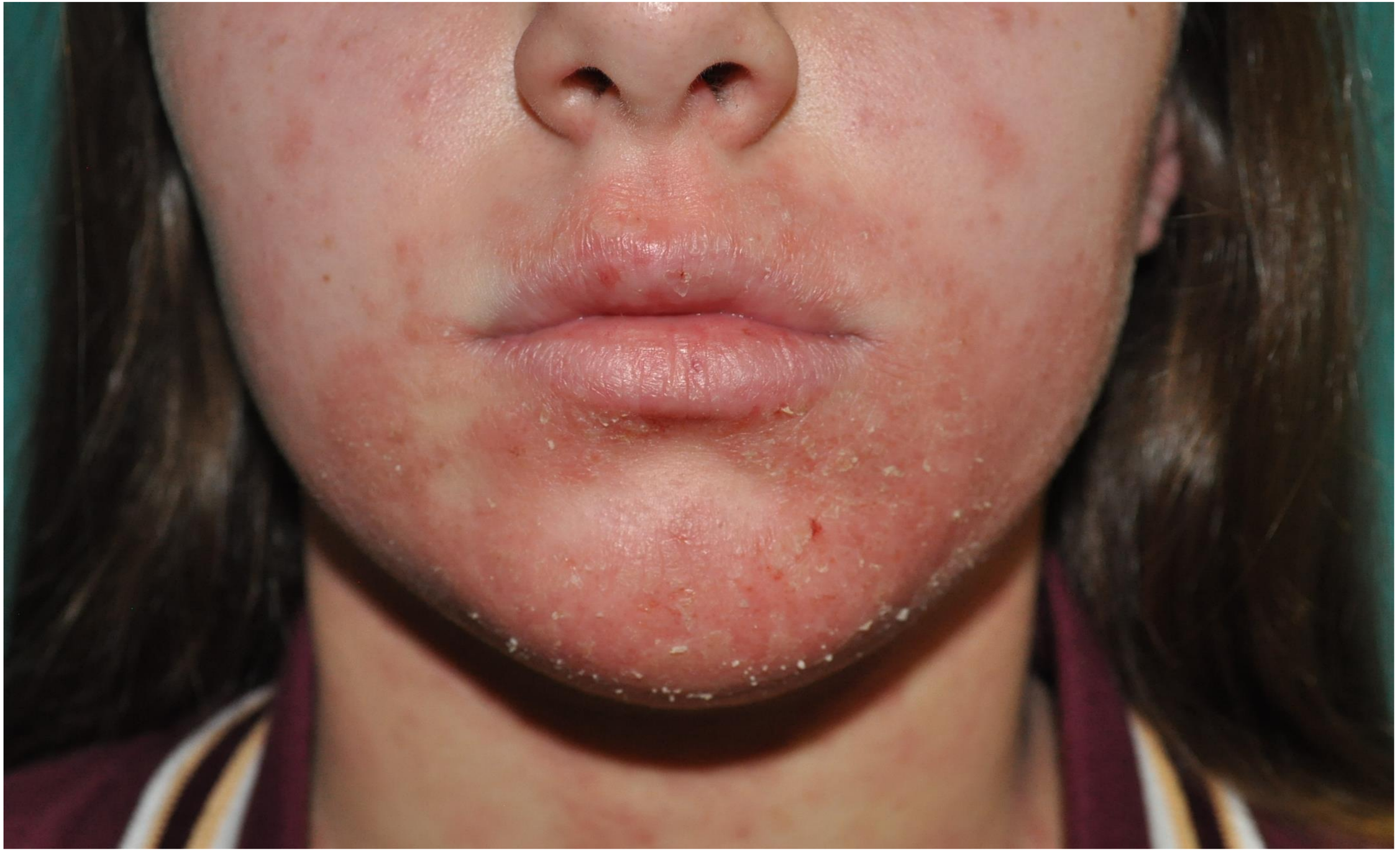
Increased expression of interleukin-23A in lesional skin of patients with atopic dermatitis with psoriasiform reaction during dupilumab treatment

Variable	Patients with DFR, Number (%)	Patients without DFR, Number (%)	P value
Gender			1.00
Female	4 (31%)	9 (69%)	
Male	3 (27%)	8 (73%)	
Age (years)			0.63
≤10	1 (17%)	5 (83%)	
11-15	3 (27%)	8 (73%)	
16-18	3 (43%)	4 (57%)	
Puberty			0.62
Pre-pubertal	1 (14%)	6 (86%)	
Post-pubertal	6 (35%)	11(65%)	
Dosing frequency			0.69
Every 1 week	1 (50%)	1 (50%)	
Every 10 days	0 (0%)	1 (100%)	
Every 2 weeks	6 (33%)	12 (67%)	
Every 4 weeks	0 (0%)	3 (100%)	
Treatment Duration (months)			0.33
≤6	2 (20%)	8 (80%)	
7-12	4 (50%)	4 (50%)	
>12	1 (17%)	5 (83%)	
Ocular Symptoms			0.29
No	6 (26%)	17 (74%)	
Yes	1 (100%)	0 (0%)	

DFR: Dupilumab facial redness







Clinical Outcomes of Dupilumab-Associated Ocular Surface Disease in the Paediatric Population

Vivien Nguyen [1], Susan Zhang [2], Shuan Dai [1]

Abstract

Background

The aim of this study is to characterise dupilumab-associated ocular surface disease (DAOSD) and its management in the paediatric population.

Methods

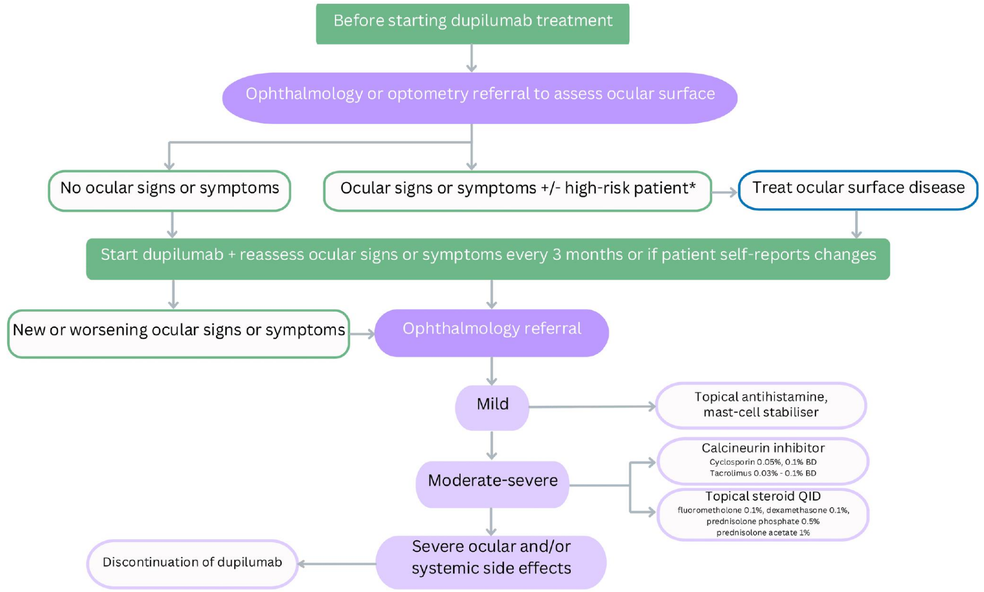
Retrospective data were obtained from the electronic medical records of a tertiary Australian paediatric public hospital's Ophthalmology department for patients reviewed between 1 January 2021 and 1 December 2024. Demographic information was recorded, including gender, age when dupilumab was started, ethnicity, dupilumab indication, past medical history, and baseline serology testing. Clinical characteristics collected included presenting visual acuity (VA), ophthalmological findings, ocular treatment, time to onset and resolution of DAOSD, and final ophthalmological outcome. Cessation of dupilumab due to DAOSD was also noted.

Results

A total of 13 patients were identified with DAOSD. The mean time from starting dupilumab to onset of DAOSD was 24 weeks (7.3-97.9 weeks). The mean time from onset of ocular symptoms to ophthalmology review was 3.6 weeks (range 0.1-8). The mean baseline VA was logMAR 0.01 (range 0-0.3). Ophthalmological examination findings included conjunctival injection (n=9, 69%), papillary reaction (n=5, 39%), superficial punctate keratitis (n=5, 39%), limbitis (n=3, 23%), and periocular involvement (n=2, 14%). Management included lubricant eye drops (n=13, 100%), topical steroid drops (n=9, 80%), topical antihistamines/mast cell stabiliser eye drops (n=5, 39%), and systemic azithromycin (n=1, 8%). The mean final VA was logMAR 0.06 (range 0-0.3). Three (23%) patients discontinued dupilumab due to ocular or systemic side effects.

Conclusions

Early ophthalmological assessment and intervention can lead to positive final visual outcomes in paediatric patients experiencing DAOSD. Future studies should investigate the long-term effects of DAOSD treatment in the paediatric population.



Characteristic		Value
Duration from dupilumab initiation to DAOSD (weeks), mean (range)		24 (7.3–97.9)
Duration from DAOSD to ophthalmic review (weeks), mean (range)		3.6 (0.1–8.0)
Ocular symptoms, n (%)[a]	Pain/discomfort	9 (69.2)
	Pruritis	4 (30.8)
	Dryness	3 (23.1)
	Photosensitivity	2 (14.4)
Ocular findings, n (%)[b]	Conjunctival injection	9 (69.2)
	Papillary reaction	5 (38.5)
	Superficial punctate keratitis	5 (38.5)
	Limbitis	3 (23.1)
	Periocular swelling	2 (14.4)
Visual acuity at first visit (logMAR), mean (range)		0.09 (0–0.3)
Ocular treatment, n (%)	Lubricating eye drops	13 (100.0)
	Corticosteroid eye drops/ointment (e.g., fluorometholone 1%, dexamethasone 0.1%, hydrocortisone 1%)	9 (69.2)
	Antihistamine/mast cell stabiliser eye drops (e.g., olopatadine 0.1%, ketotifen 1.0%)	5 (38.5)
	Oral antibiotics	1 (7.7)
Visual acuity at resolution visit (logMAR), mean (range)		0.06 (0–0.3)
Duration to DAOSD stability/resolution (weeks), mean (range)		9.9 (2.7–20.8)

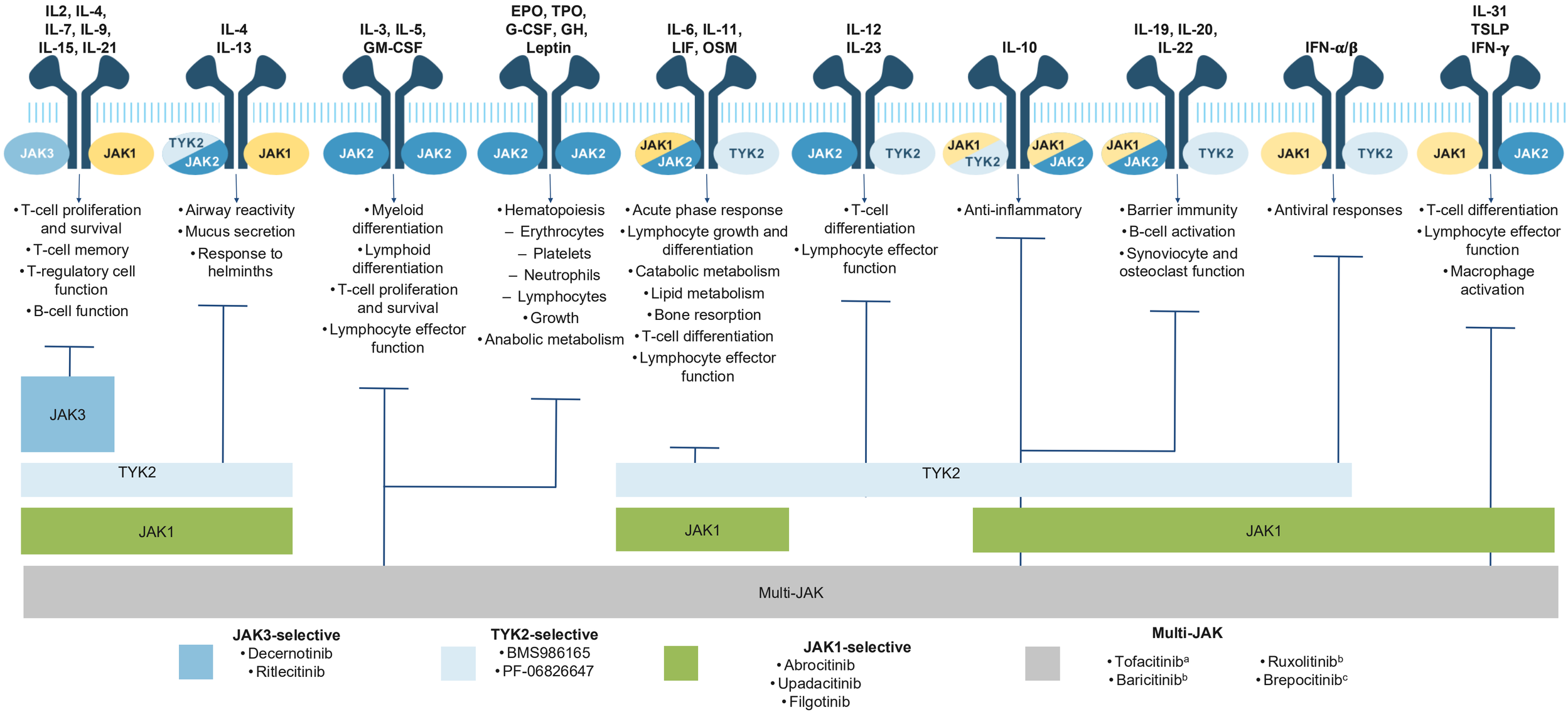
Availability of drugs for children

Age and comorbidities as limiting factors

Drug	Age of approval	Remarks
Biologics		
Dupilumab	> 6 months	Prurigo nodularis, Asthma, Nasal polyposis, Eosinophilic esophagitis
Tralokinumab	> 12 years	Ongoing evaluation > 6 months
Lebrikizumab	> 12 years	Ongoing evaluation > 6 months
Nemolizumab	> 12 years	Prurigo nodularis; ongoing evaluation > 2 years

Current EMA-approved biologic therapies for AD

Potential Target of JAK Inhibition[1]



EPO=erythropoietin; GM-CSF=granulocyte-macrophage colony-stimulating factor; G-CSF=granulocyte colony-stimulating factor; GH=growth hormone; LIF=leukemia inhibitory factor; TPO=thyroperoxidase.
[a]JAK1/3; [b]JAK1/2; [c]JAK1/TYK2.[1]

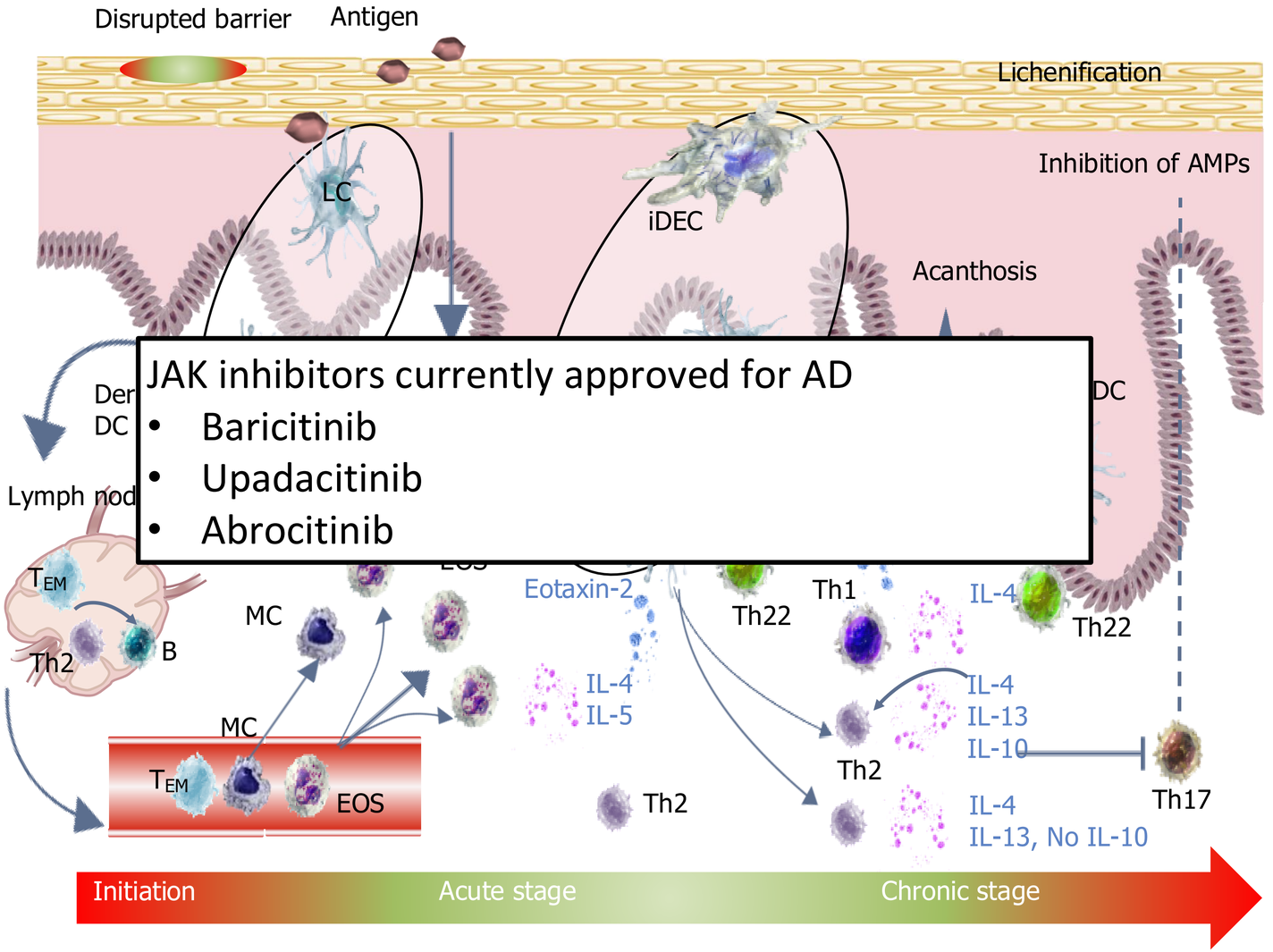
1. Schwartz DM, et al. *Nat Rev Drug Discov.* 2017;16(12):843-862. Erratum in: *Nat Rev Drug Discov.* 2017;17(1):78. **2.** Wollenhaupt J, et al. *J Rheumatol.* 2014;41(5):837-852.

The relevance of specific JAK combinations for therapeutic efficacy is unknown.[2]

Cytokine signaling relevant in AD

JAK/STAT pathway involves multiple cytokines important in AD

- TSLP
- IL-4
- IL-5
- IL-10
- IL-13
- IL-22



AD=atopic dermatitis; IL=interleukin; JAK=Janus kinase; Th=T helper cell; TSLP=thymic stromal lymphopoietin

1. O'Shea JJ et al. Nat Rev Rheumatol 2013;9(3)173-82; 2. Zhong J et al. Database (Oxford) 2014;2014:bau007; 3. Guttman-Yassky E et al. Expert Opin Biol Ther 2013;13:549-61

CLINICAL TRIAL

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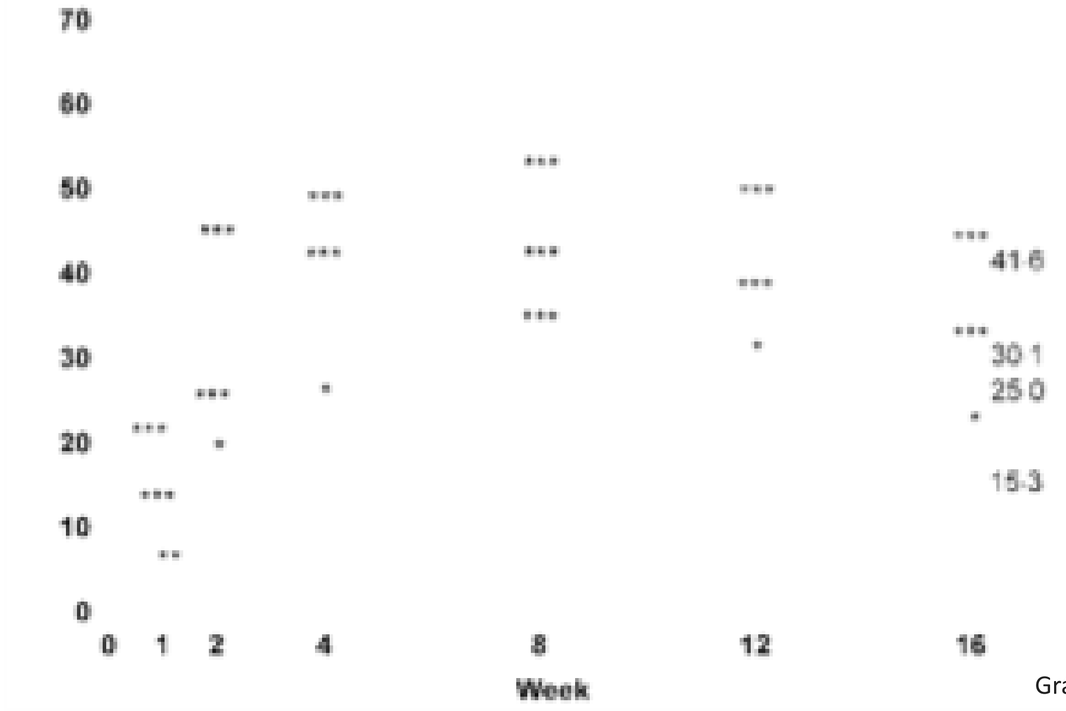
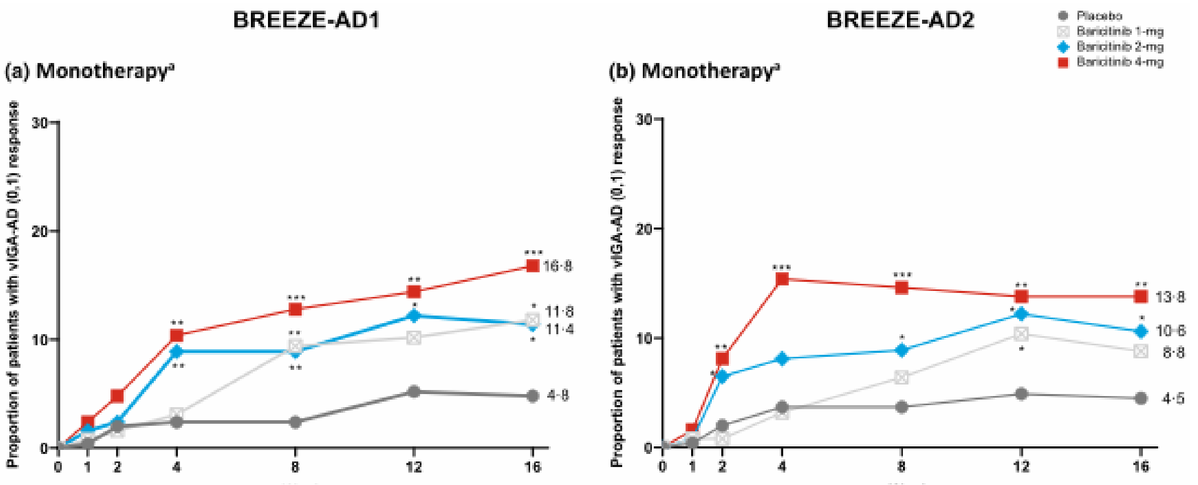
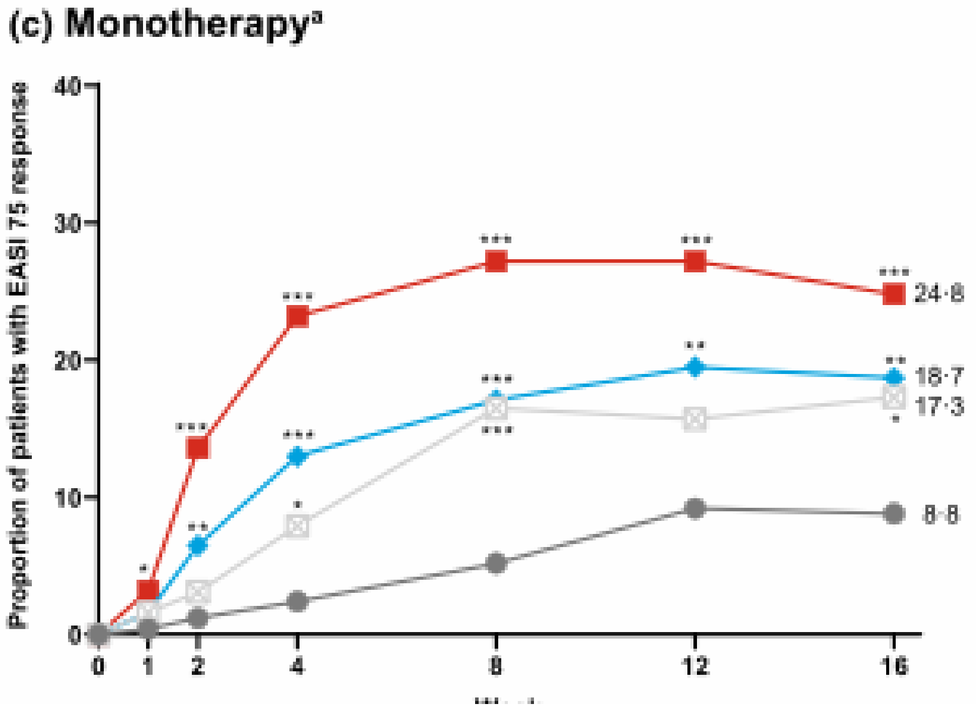
British Journal of Dermatology

Baricitinib in patients with moderate-to-severe atopic dermatitis and inadequate response to topical corticosteroids: results from two randomized monotherapy phase III trials

EL. Simpson,[1] J-P. Lacour,[2] L. Spelman,[3] R. Galimberti,[4] LF. Eichenfield,[5] R. Bissonnette,[6] B.A. King,[7] JP. Thyssen,[8] J.I. Silverberg,[9] T. Bieber,[10] K. Kabashima,[11] Y. Tsunemi,[12] A. Costanzo,[13] E. Guttman-Yassky,[14] L.A. Beck,[15] J.M. Janes,[16] A.M. DeLozier,[16] M. Gamalo,[16] D.R. Brinker,[16] T. Cardillo,[16] F.P. Nunes,[16] A.S. Paller,[17] A. Wollenberg[18] and K. Reich[19,20]





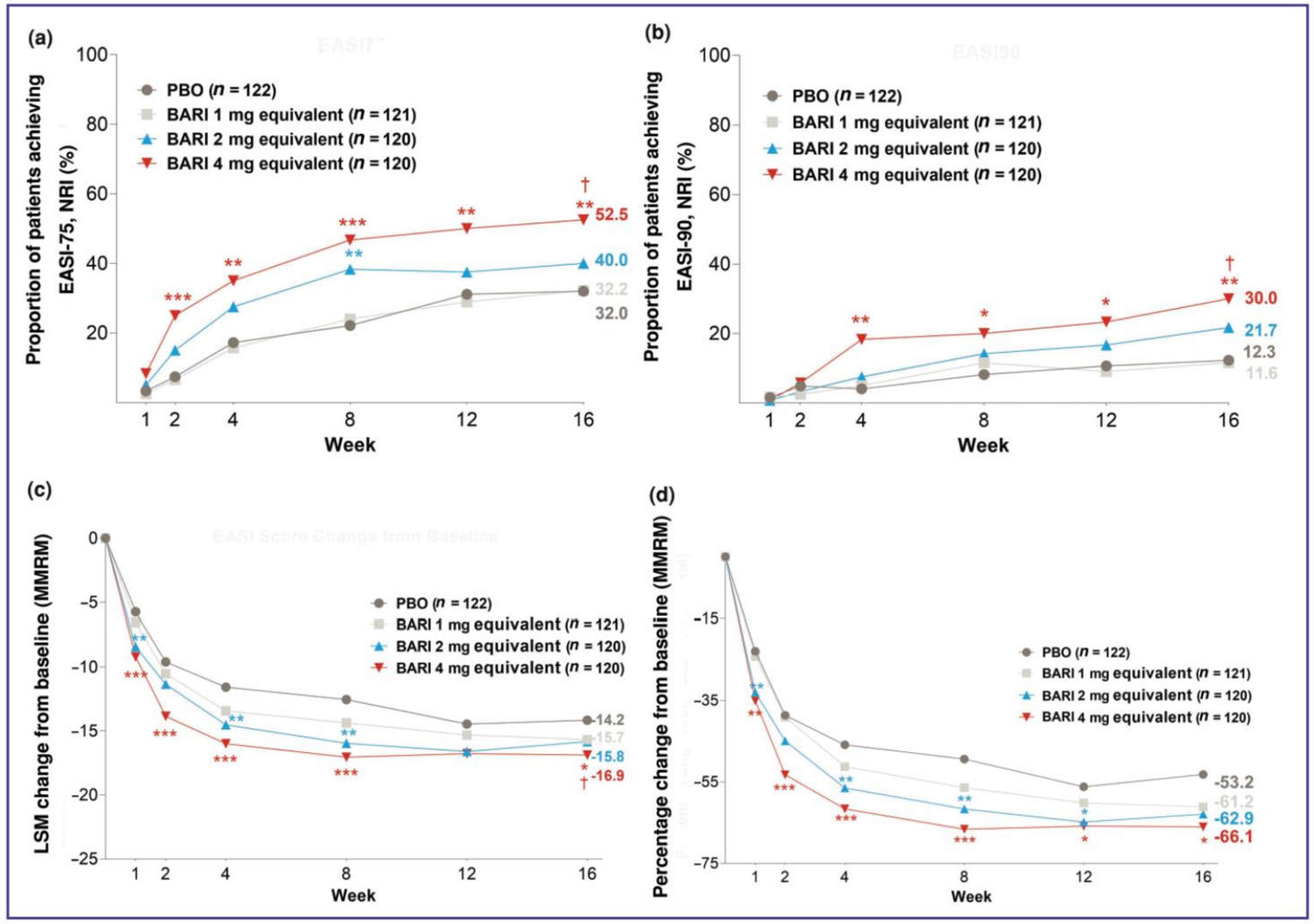


Gráficas extraídas de Simpson EL, et al. Br J Dermatol. 2020

Simpson EL, Lacour JP, Spelman Let al. Baricitinib in patients with moderate-to-severe atopic dermatitis and inadequate response to topical corticosteroids: results from two randomized monotherapy phase III trials. Br J Dermatol. 2020 Aug;183(2):242-255. doi: 10.1111/bjd.18898. Epub 2020 Mar 5. PMID: 31995838.

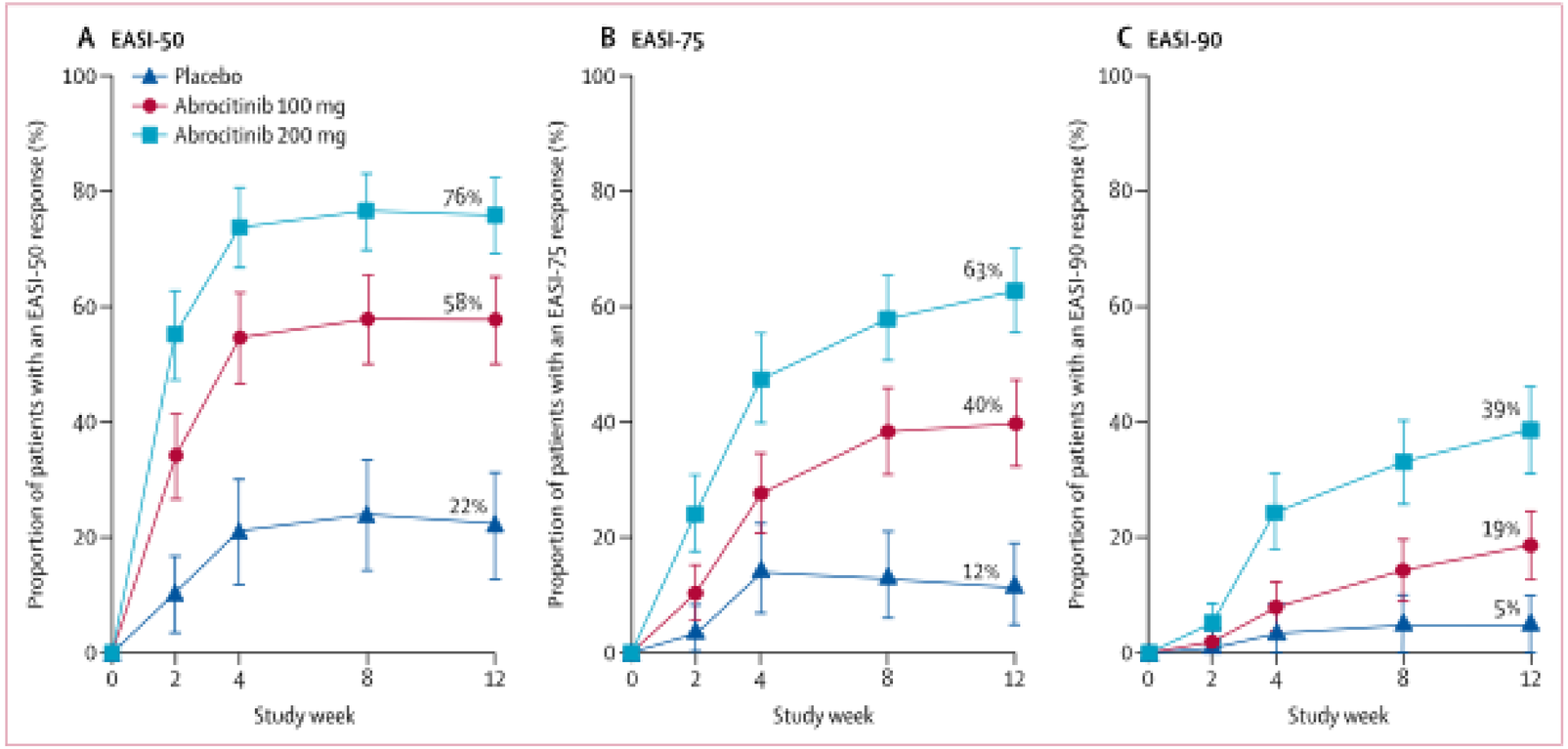
Efficacy and safety of baricitinib in combination with topical corticosteroids in paediatric patients with moderate-to-severe atopic dermatitis with an inadequate response to topical corticosteroids: results from a phase III, randomized, double-blind, placebo-controlled study (BREEZE-AD PEDS)

Antonio Torrelo,[1] Barbara Rewerska,[2] Maria Galimberti,[3] Amy Paller,[4] Chin-Yi Yang,[5,6] Apurva Prakash,[7] Danting Zhu,[7] Marco Antonio G. Pontes Filho,[7] Wen-Shuo Wu[7] and Lawrence F. Eichenfield[8]



Efficacy and safety of abrocitinib in adults and adolescents with moderate-to-severe atopic dermatitis (JADE MONO-1): a multicentre, double-blind, randomised, placebo-controlled, phase 3 trial

Eric L Simpson, Rodney Sinclair, Seth Forman, Andreas Wollenberg, Roland Aschoff, Michael Cork, Thomas Bieber, Jacob P Thyssen, Gil Yosipovitch, Carsten Flohr, Nina Magnolo, Catherine Maari, Claire Feeney, Pinaki Biswas, Svitlana Tatulych, Hernan Valdez, Ricardo Rojo



	Placebo (n=77)	Abrocitinib 100 mg (n=156)	Abrocitinib 200 mg (n=154)
Deaths	0	0	0
Serious adverse events	3 (4%)	5 (3%)	5 (3%)
Most frequently reported treatment-emergent adverse events (≥5% in any treatment group)			
Nausea	2 (3%)	14 (9%)	31 (20%)
Nasopharyngitis	8 (10%)	23 (15%)	18 (12%)
Headache	2 (3%)	12 (8%)	15 (10%)
Upper respiratory tract infection	5 (7%)	11 (7%)	11 (7%)
Atopic dermatitis	13 (17%)	22 (14%)	8 (5%)
Treatment-emergent herpes viral infection			
Any	0	5 (3%)	4 (3%)
Herpes simplex	0	1 (1%)	3 (2%)
Herpes zoster	0	1 (1%)	2 (1%)
Oral herpes	0	3 (2%)	1 (1%)
Eczema herpeticum	1 (1%)	2 (1%)	0

Data are n (%).

Table 3: Adverse events

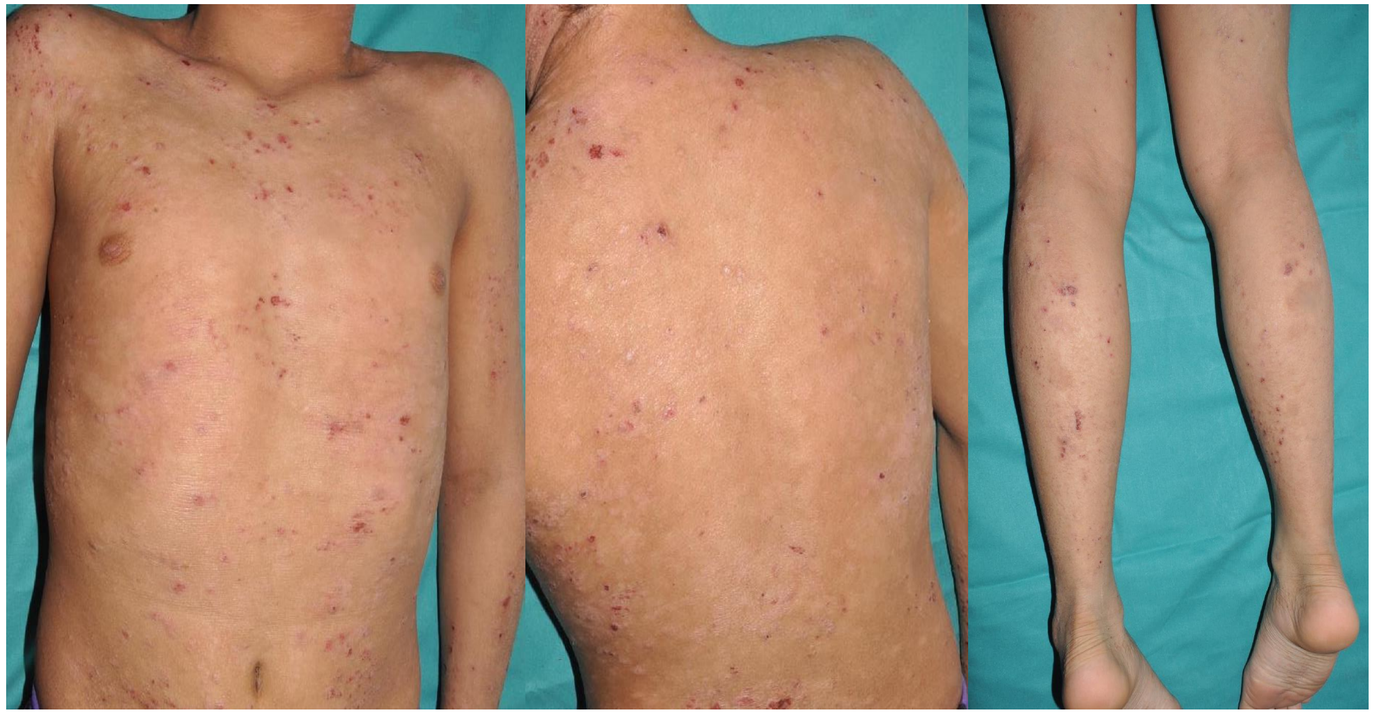
	Placebo (n=77)	Abrocitinib 100 mg (n=156)	Abrocitinib 200 mg (n=154)
General disorders and administration site conditions or condition aggravated	1 (1%)	0	0
Appendicitis	1 (%)	0	0
Meniscal degeneration	1 (1%)	0	0
Atopic dermatitis	1 (1%)	0	0
Appendicitis	0	1 (1%)	0
Dizziness	0	1 (%)	0
Seizure	0	1 (1%)	0
Retinal detachment	0	1 (1%)	0
Acute pancreatitis	0	1 (1%)*	0
Inflammatory bowel disease	0	0	1 (1%)*
Peritonsillitis	0	0	1 (1%)
Dehydration	0	0	1 (1%)
Asthma	0	0	2 (1%)

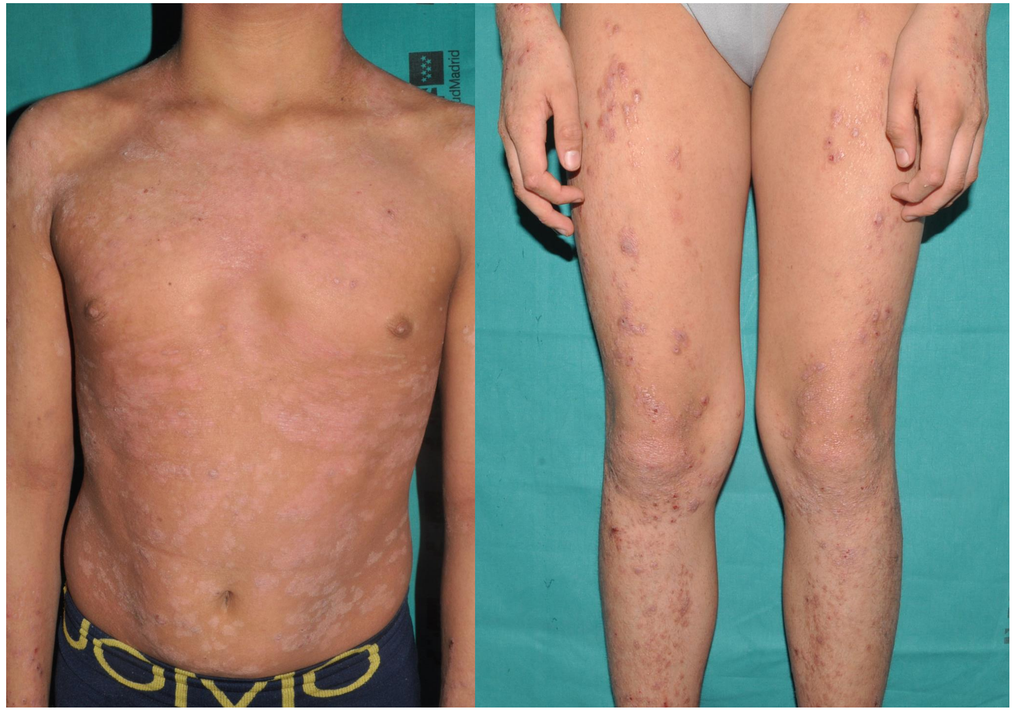
Data are n (%). *Serious adverse event related to treatment.

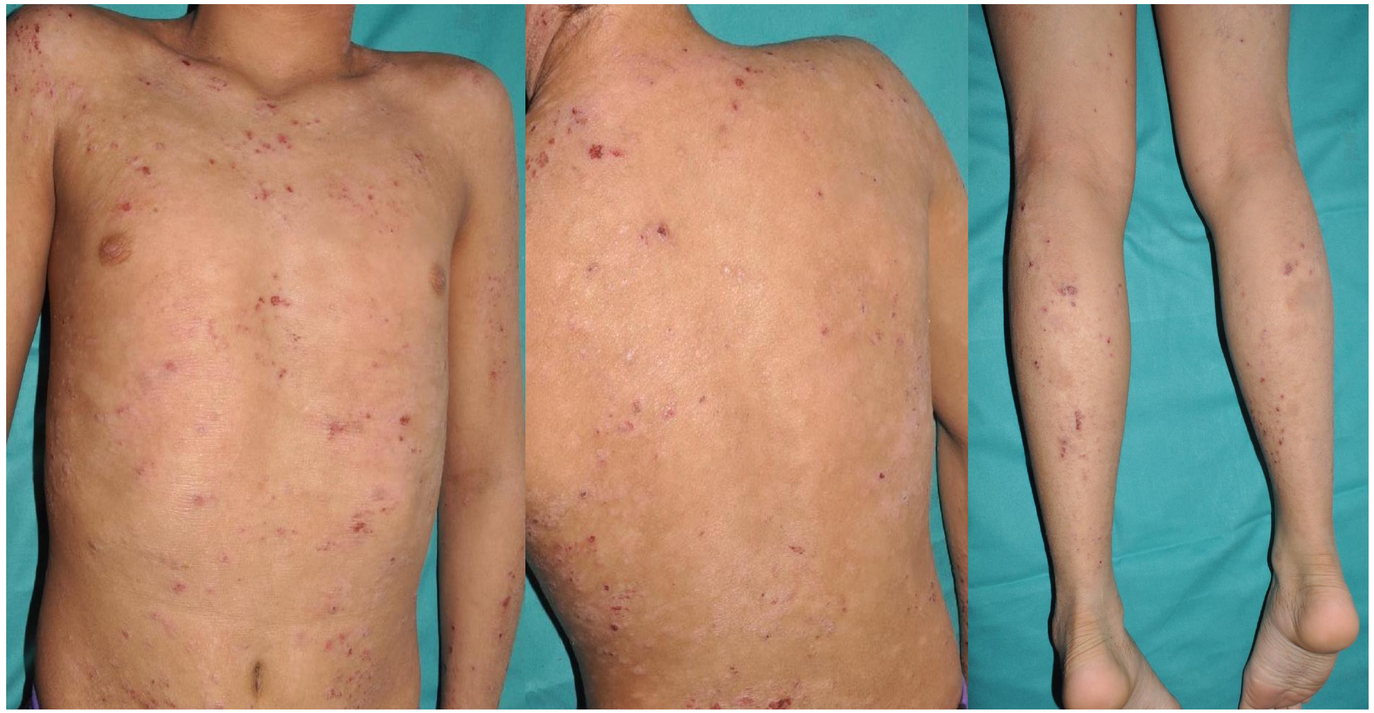
Table 4: Serious adverse events

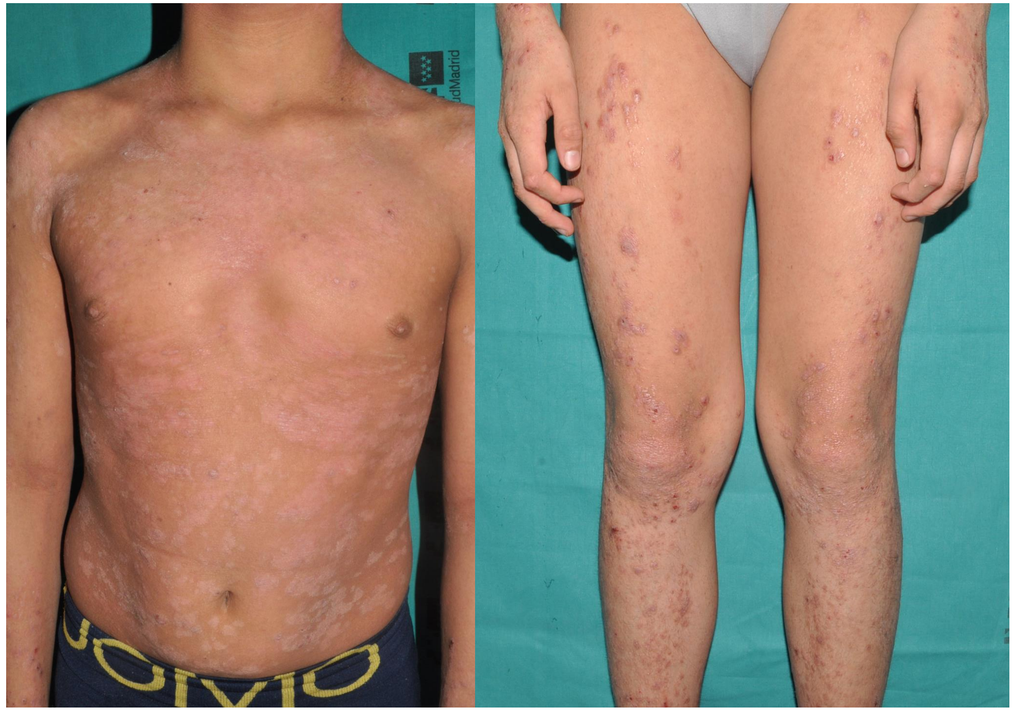
Tabla y gráficas extraídas de Simpson EL et al. Lancet. 2020

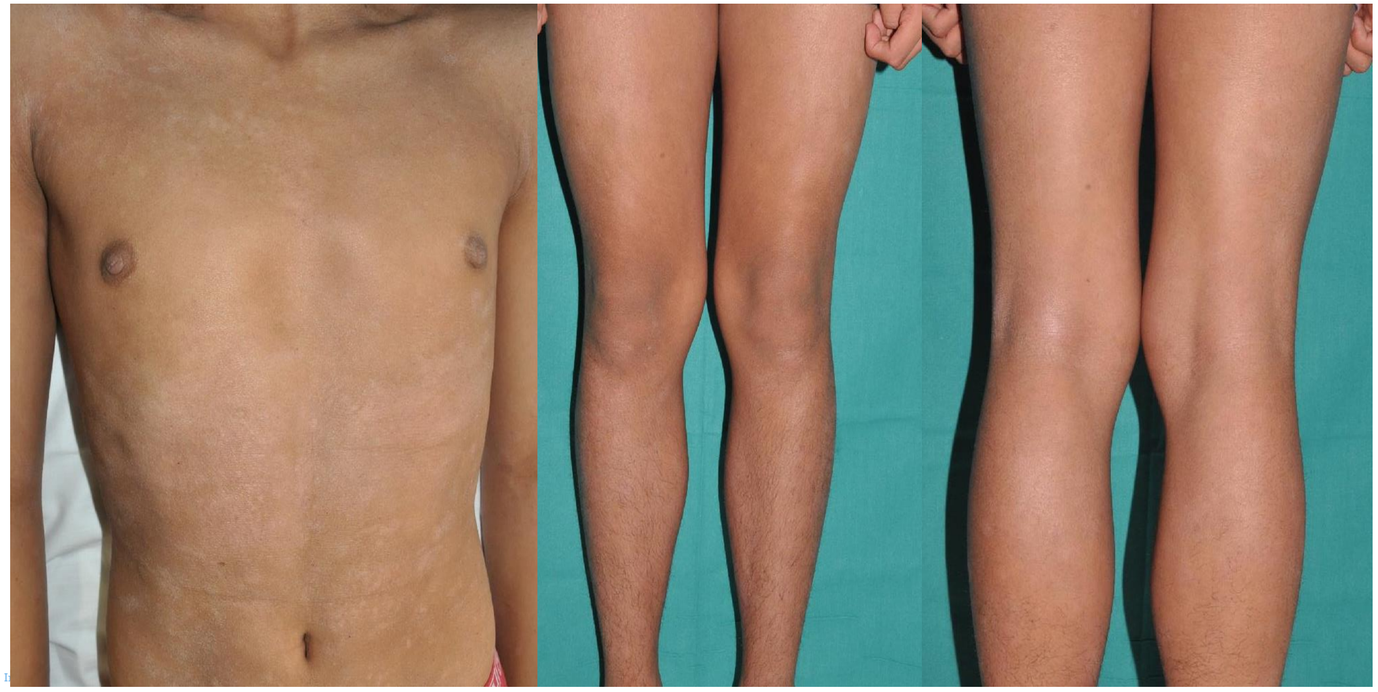
Simpson EL, Sinclair R, Forman S, Wollenberg A, Aschoff R, Cork M, Bieber T, Thyssen JP, Yosipovitch G, Flohr C, Magnolo N, Maari C, Feeney C, Biswas P, Tatulych S, Valdez H, Rojo R. Efficacy and safety of abrocitinib in adults and adolescents with moderate-to-severe atopic dermatitis (JADE MONO-1): a multicentre, double-blind, randomised, placebo-controlled, phase 3 trial. Lancet. 2020 Jul 25;396(10246):255-266. doi: 10.1016/S0140-6736(20)30732-7. PMID: 32711801.

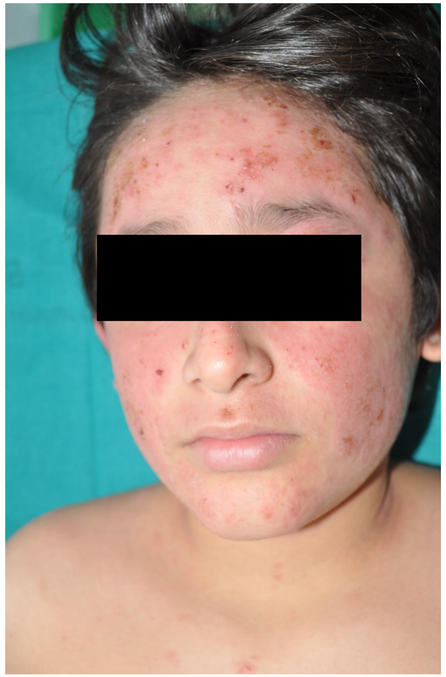
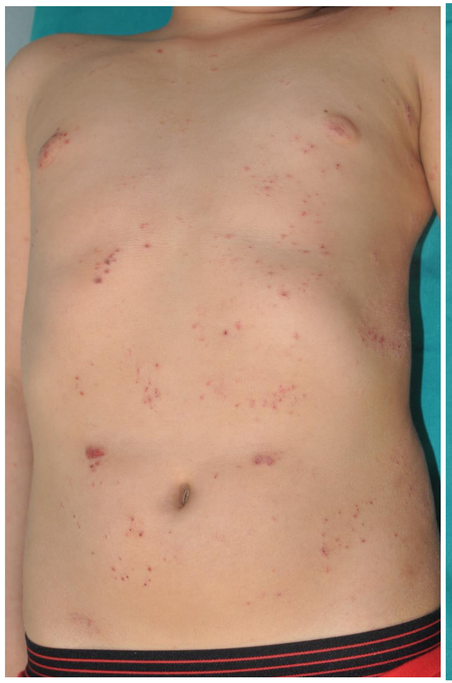
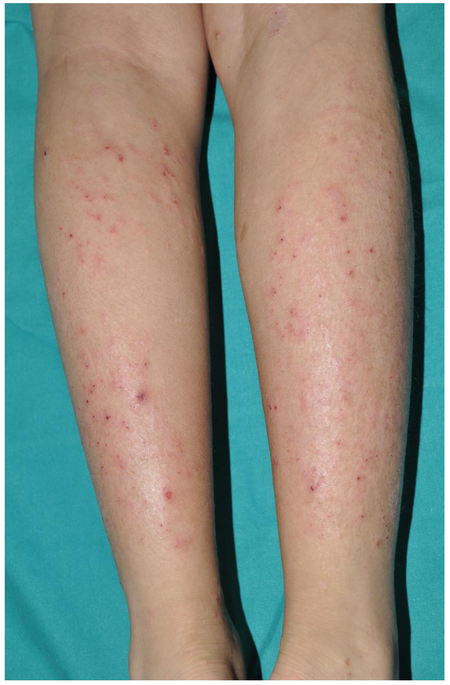
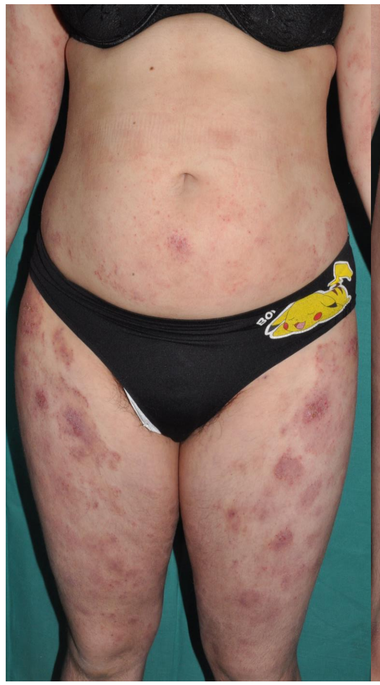


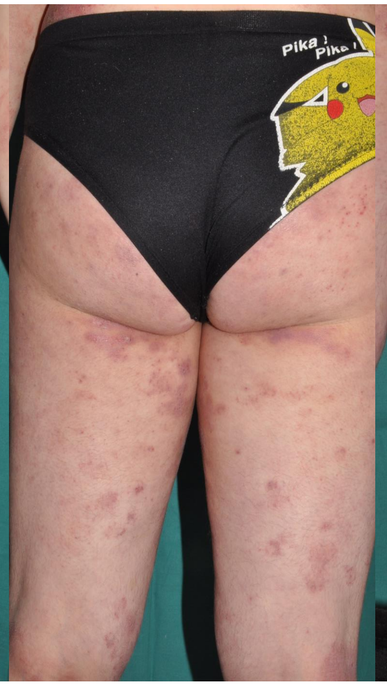


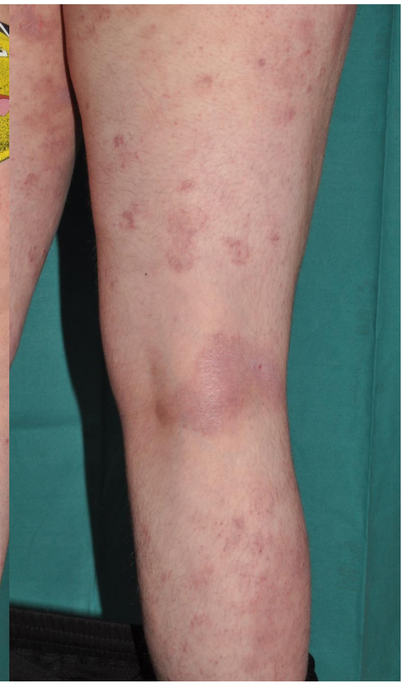


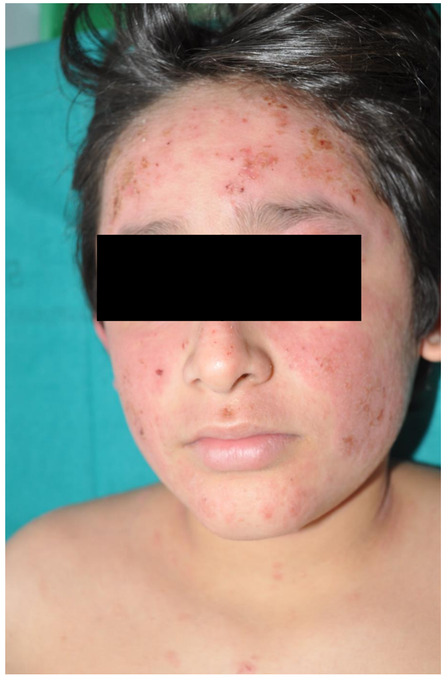
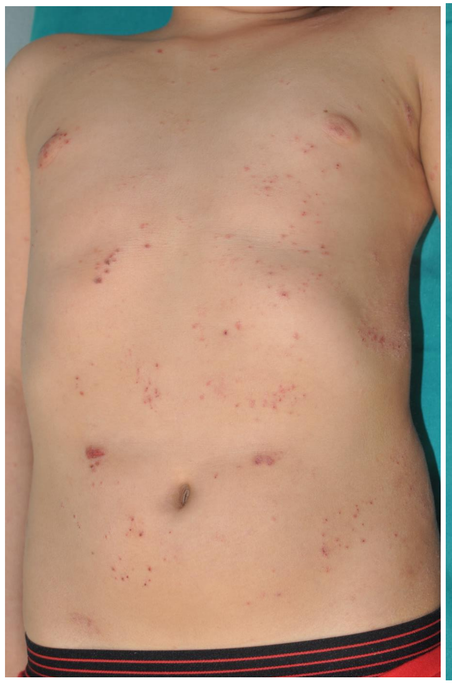
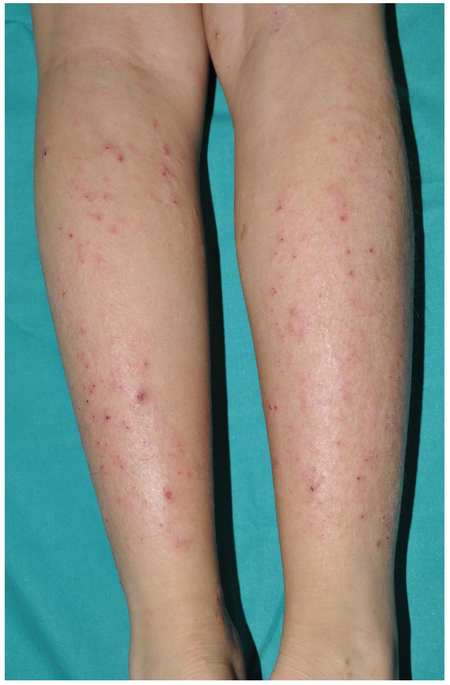
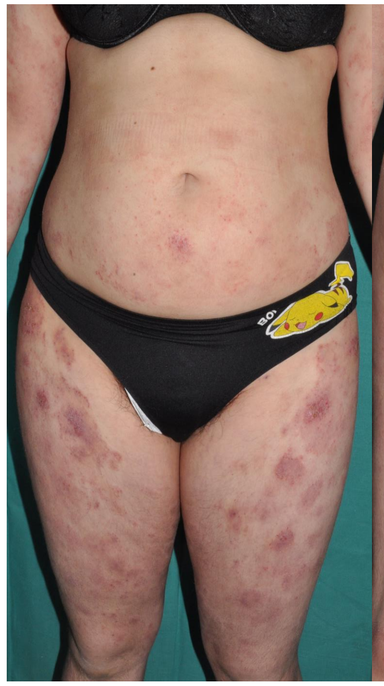


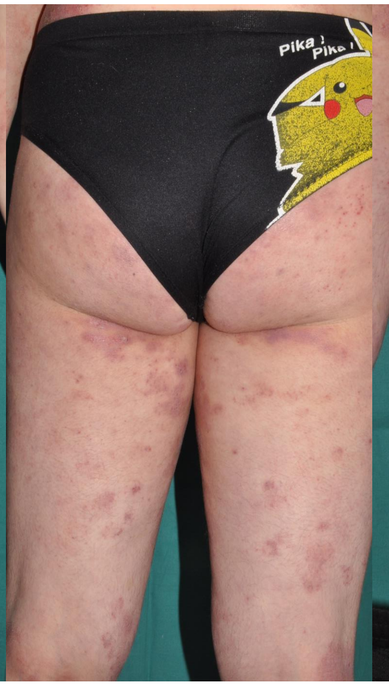
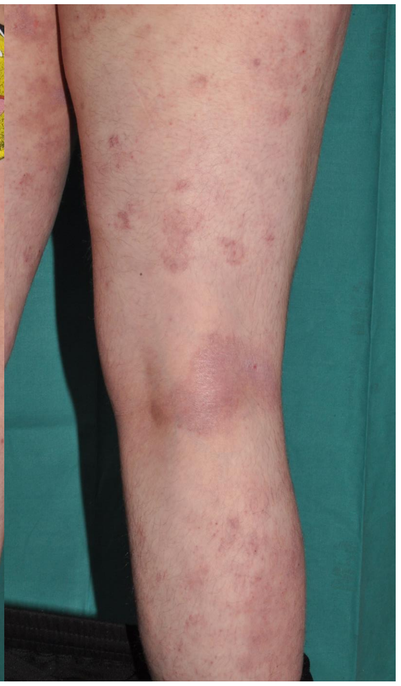
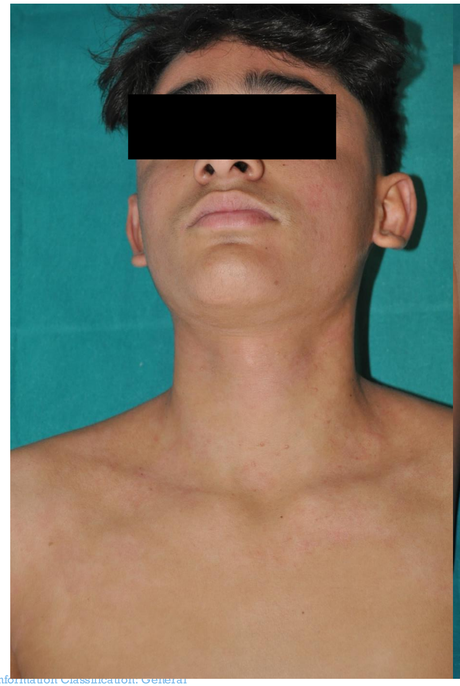
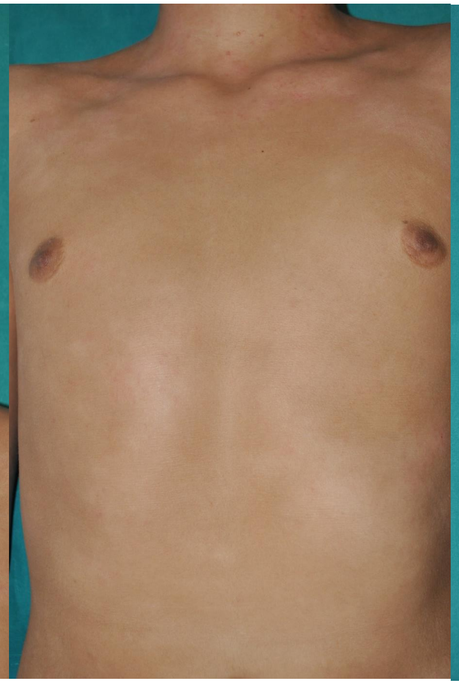
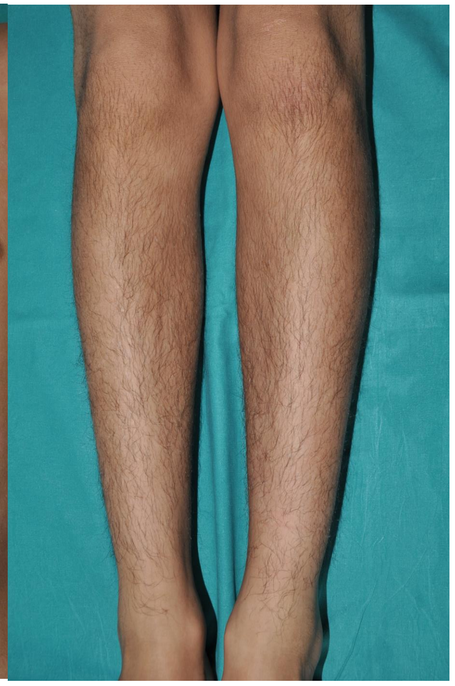
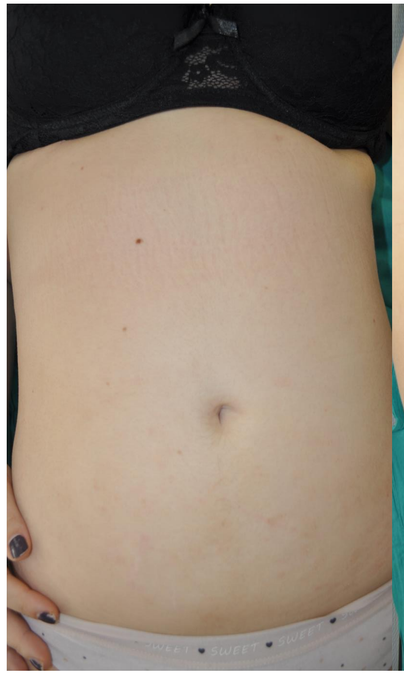
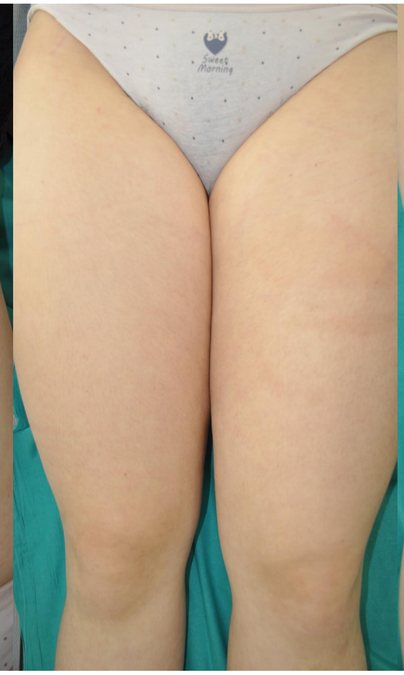
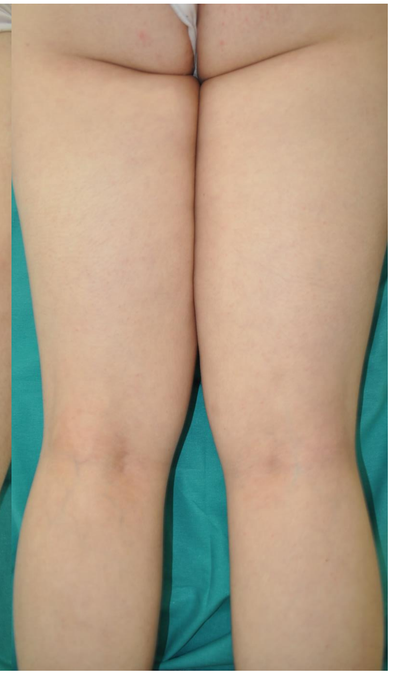






Selecting the best treatment for each patient

RESEARCH ARTICLE

Comparative efficacy and safety of dupilumab versus newly approved biologics and JAKi in pediatric atopic dermatitis: A systematic review and network meta-analysis

Qiwei Liao*, Hanwen Pan, Yixin Guo, Yuxiang Lan, Zhuo Huang, Peiyi Wu

Foshan Clinical Medical School of Guangzhou University of Chinese Medicine, Foshan, Guangdong, China

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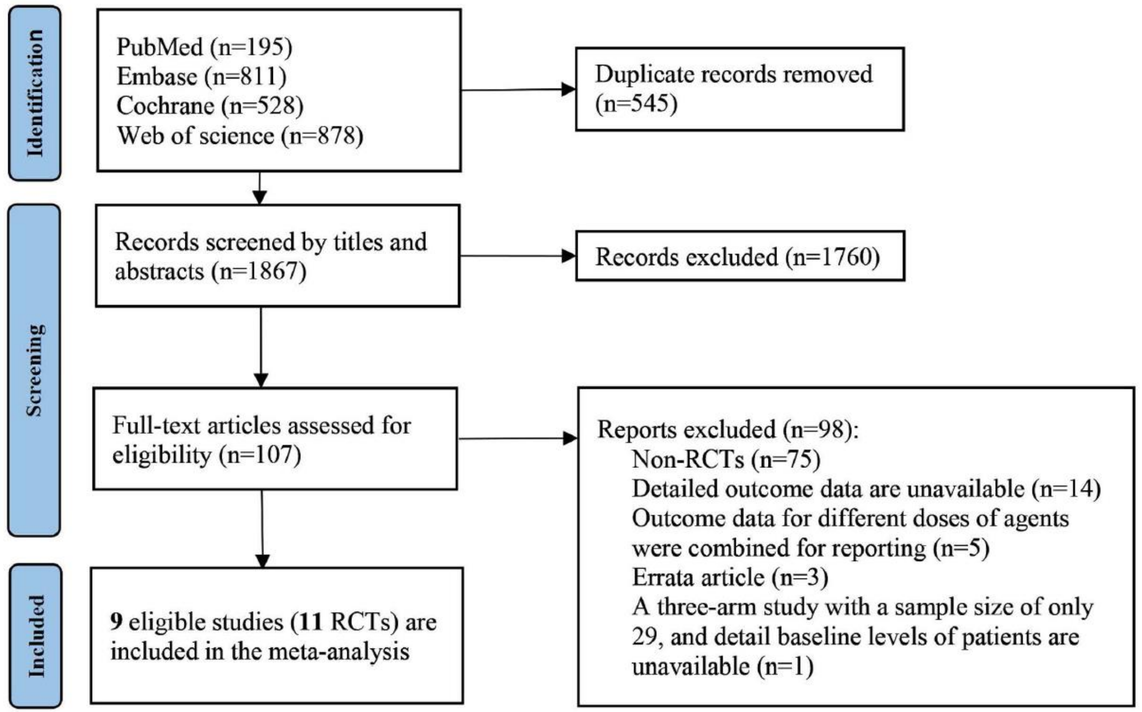


Conclusion

In summary, current evidence indicates that upadacitinib (30 mg) is the most effective biological therapy for treating adolescent AD. Delgocitinib (0.25% and 0.5%) and tralokinumab (150 mg and 300 mg) demonstrate efficacy comparable to that of dupilumab (300 mg). Nemolizumab (30 mg) offers certain advantages in alleviating pruritus. Moreover, the safety profiles of the 7 agents included in this study for pediatric AD are comparable to those observed in adult AD. The favorable efficacy-risk ratio of biologics and JAKi indicates that they can provide valuable support in the treatment of pediatric AD.

JAMA Dermatology | Original Investigation

Efficacy and Safety of Upadacitinib vs Dupilumab in Adults With Moderate-to-Severe Atopic Dermatitis

A Randomized Clinical Trial

Andrew Blauvelt, MD, MBA; Henrique D. Teixeira, PhD, MBA; Eric L. Simpson, MD, MCR; Antonio Costanzo, MD; Marjolein De Bruin-Weller, MD; Sebastien Barbarot, MD, PhD; Vimal H. Prajapati, MD; Peter Lio, MD; Xiaofei Hu, PhD; Tianshuang Wu, PhD; John Liu, MD, MS; Barry Ladizinski, MD, MPH, MBA; Alvina D. Chu, MD; Kilian Eyerich, MD

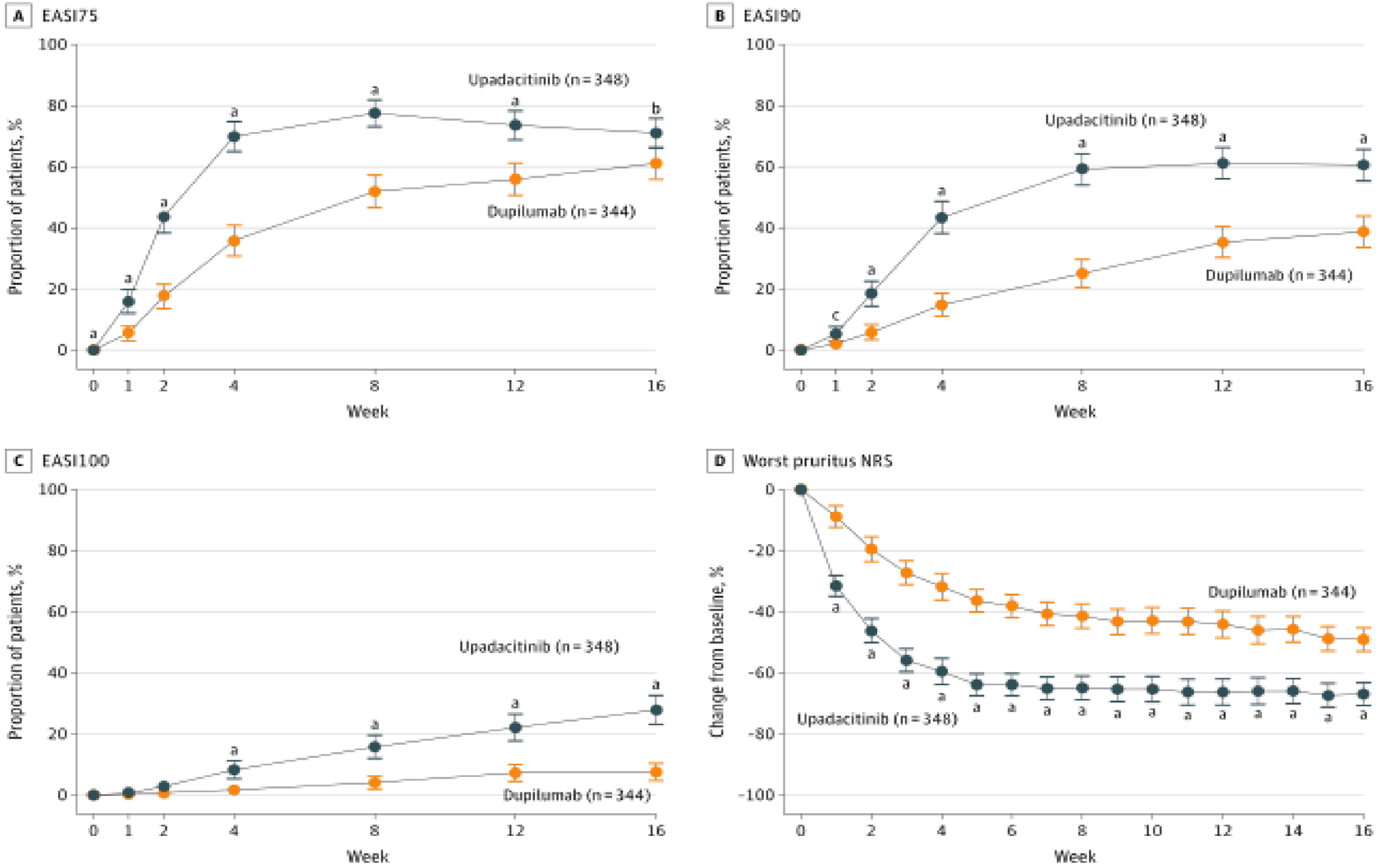


Tabla y gráficas extraídas de Blauvelt A, et al. JAMA Dermatol. 2021

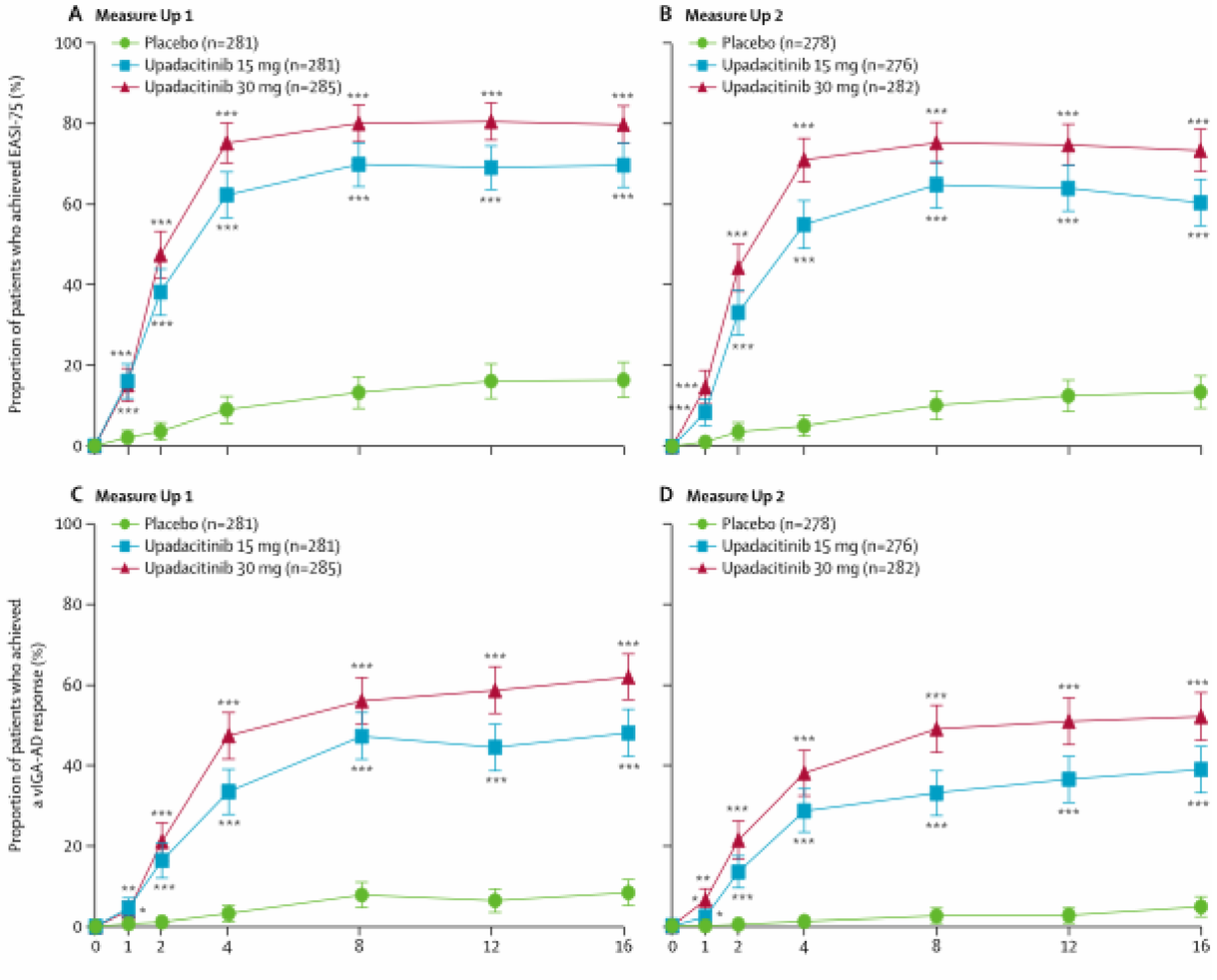
Table 3. TEAEs Through Week 16 for All Patients Receiving 1 Dose or More of Study Drug

TEAE	Patients, No. (%)	
	Dupilumab, 300 mg (n = 344)	Upadacitinib, 30 mg (n = 348)
AE	216 (62.8)	249 (71.6)
AE with reasonable possibility of being drug-related[a]	122 (35.5)	153 (44.0)
Severe AE	14 (4.1)	25 (7.2)
SAE	4 (1.2)	10 (2.9)
SAE with reasonable possibility of being drug related[a]	2 (0.6)	4 (1.1)
AE leading to discontinuation of study drug	4 (1.2)	7 (2.0)
AE leading to death[b]	0	1 (0.3)
AEs of special interest		
Serious infections	2 (0.6)	4 (1.1)
Opportunistic infection, excluding tuberculosis and herpes zoster[c]	0	1 (0.3)
Herpes zoster	3 (0.9)	7 (2.0)
Active tuberculosis	0	0
Nonmelanoma skin cancer[d]	1 (0.3)	0
Malignant neoplasm, excluding NMSC	0	0
Lymphoma	0	0
Hepatic disorder[e]	4 (1.2)	10 (2.9)
Adjudicated gastrointestinal perforations	0	0
Anemia	1 (0.3)	7 (2.0)
Neutropenia	2 (0.6)	6 (1.7)
Lymphopenia	0	2 (0.6)
Creatine phosphokinase elevation	10 (2.9)	23 (6.6)
Renal dysfunction	1 (0.3)	1 (0.3)
Adjudicated major adverse cardiovascular events	0	0
Adjudicated venous thromboembolic events	0	0
TEAEs reported by ≥5% in either treatment group		
Acne[f]	9 (2.6)	55 (15.8)
Dermatitis atopic	29 (8.4)	24 (6.9)
Upper respiratory tract infection	13 (3.8)	22 (6.3)
Blood CPK level increased	10 (2.9)	23 (6.6)
Nasopharyngitis	22 (6.4)	20 (5.7)
Headache	21 (6.1)	14 (4.0)
Conjunctivitis	29 (8.4)	5 (1.4)

Blauvelt A, Teixeira HD, Simpson EL, Costanzo A, De Bruin-Weller M, Barbarot S, Prajapati VH, Lio P, Hu X, Wu T, Liu J, Ladizinski B, Chu AD, Eyerich K. Efficacy and Safety of Upadacitinib vs Dupilumab in Adults With Moderate-to-Severe Atopic Dermatitis: A Randomized Clinical Trial. JAMA Dermatol. 2021 Sep 1;157(9):1047-1055. doi: 10.1001/jamadermatol.2021.3023. PMID: 34347860; PMCID: PMC8340015.

Once-daily upadacitinib versus placebo in adolescents and adults with moderate-to-severe atopic dermatitis (Measure Up 1 and Measure Up 2): results from two replicate double-blind, randomised controlled phase 3 trials

Emma Guttman-Yassky, Henrique D Teixeira, Eric L Simpson, Kim A Papp, Aileen L Pangan, Andrew Blauvelt, Diamant Thaçi, Chia-Yu Chu, H Chih-ho Hong, Norito Katoh, Amy S Paller, Brian Calimlim, Yihua Gu, Xiaofei Hu, Meng Liu, Yang Yang, John Liu, Allan R Tenorio, Alvina D Chu, Alan D Irvine



	Upadacitinib 15 mg		Upadacitinib 30 mg		Placebo	
	Measure Up 1 (n=281)	Measure Up 2 (n=276)	Measure Up 1 (n=285)	Measure Up 2 (n=282)	Measure Up 1 (n=281)	Measure Up 2 (n=278)
Any treatment-emergent adverse event	176 (63%)	166 (60%)	209 (73%)	173 (61%)	166 (59%)	146 (53%)
Serious adverse events	6 (2%)	5 (2%)	8 (3%)	7 (3%)	8 (3%)	8 (3%)
Adverse events leading to discontinuation of study drug	4 (1%)	11 (4%)	11 (4%)	7 (3%)	12 (4%)	12 (4%)
Deaths	0	0	0	0	0	0
Adverse events of special interest						
Serious infections	2 (1%)	1 (<1%)	2 (1%)	2 (1%)	0	2 (1%)
Opportunistic infection (excluding tuberculosis and herpes zoster)	0	3 (1%)	3 (1%)	0	4 (1%)	0
Eczema herpeticum	0	3 (1%)	3 (1%)	0	4 (1%)	0
Herpes zoster	5 (2%)	6 (2%)	6 (2%)	3 (1%)	0	2 (1%)
Active tuberculosis	0	0	0	0	0	0
Non-melanoma skin cancer	1 (<1%)*	2 (1%)†	0	0	0	0
Malignancy other than non-melanoma skin cancer	0	0	2 (1%)‡	1 (<1%)§	0	0
Lymphoma	0	0	0	0	0	0
Hepatic disorder	5 (2%)	2 (1%)	8 (3%)	4 (1%)	2 (1%)	4 (1%)
Adjudicated gastrointestinal perforations	0	0	0	0	0	0
Anaemia	1 (<1%)	2 (1%)	5 (2%)	4 (1%)	1 (<1%)	2 (1%)
Neutropenia	4 (1%)	2 (1%)	15 (5%)	6 (2%)	2 (1%)	1 (<1%)
Lymphopenia	1 (<1%)	0	2 (1%)	1 (<1%)	2 (1%)	0
Renal dysfunction	0	0	0	0	0	0
Adjudicated major adverse cardiovascular event	0	0	0	0	0	0
Adjudicated venous thromboembolic event	0	0	0	0	0	1 (<1%)
Most frequently reported treatment-emergent adverse events (≥5% in any treatment group)						
Acne¶	19 (7%)	35 (13%)	49 (17%)	41 (15%)	6 (2%)	6 (2%)
Upper respiratory tract infection	25 (9%)	19 (7%)	38 (13%)	17 (6%)	20 (7%)	12 (4%)
Nasopharyngitis	22 (8%)	16 (6%)	33 (12%)	18 (6%)	16 (6%)	13 (5%)
Headache	14 (5%)	18 (7%)	19 (7%)	20 (7%)	12 (4%)	11 (4%)
Plasma creatine phosphokinase elevation	16 (6%)	9 (3%)	16 (6%)	12 (4%)	7 (3%)	5 (2%)
Atopic dermatitis	9 (3%)	8 (3%)	4 (1%)	4 (1%)	26 (9%)	26 (9%)

Data are n (%). *A case of squamous cell cancer. †Includes one case of squamous cell cancer and one case of basal cell cancer. ‡Includes one case of breast cancer and one case of gastric cancer. §A case of anal cancer. ¶Approximately 75% of the acne cases were mild, some were moderate, and one severe event was reported.

Table 3: Treatment-emergent adverse events in the safety population

Tabla y gráficas extraídas de Guttman-Yassky E, et al. Lancet. 2021

Guttman-Yassky E, Teixeira HD, Simpson EL, Papp KA, Pangan AL, Blauvelt A, Thaçi D, Chu CY, Hong HC, Katoh N, Paller AS, Calimlim B, Gu Y, Hu X, Liu M, Yang Y, Liu J, Tenorio AR, Chu AD, Irvine AD. Once-daily upadacitinib versus placebo in adolescents and adults with moderate-to-severe atopic dermatitis (Measure Up 1 and Measure Up 2): results from two replicate double-blind, randomised controlled phase 3 trials. Lancet. 2021 Jun 5;397(10290):2151-2168. doi: 10.1016/S0140-6736(21)00588-2. Epub 2021 May 21. Erratum in: Lancet. 2021 Jun 5;397(10290):2150. PMID: 34023008.

Abrocitinib versus Placebo or Dupilumab for Atopic Dermatitis

T. Bieber, E.L. Simpson, J.I. Silverberg, D. Thaçi, C. Paul, A.E. Pink, Y. Kataoka, C.-Y. Chu, M. DiBonaventura, R. Rojo, J. Antinew, I. Ionita, R. Sinclair, S. Forman, J. Zdybski, P. Biswas, B. Malhotra, F. Zhang, and H. Valdez, for the JADE COMPARE Investigators*

Table 2. Summary of Adverse Events

Event	No. (%)		
		Abrocitinib	
	Placebo (n = 96)	100 mg (n = 95)	200 mg (n = 94)
TEAEs of any causality	50 (52.1)	54 (56.8)	59 (62.8)
Serious AEs of any causality	2 (2.1)	0	1 (1.1)
Severe AEs of any causality	2 (2.1)	0	2 (2.1)
TEAEs of any causality that led to treatment discontinuation	2 (2.1)	1 (1.1)	2 (2.1)
Deaths	0	0	0
Most frequently reported TEAEs of any causality (≥3% in any treatment group)			
Nausea	1 (1.0)	7 (7.4)	17 (18.1)
Upper respiratory tract infection	10 (10.4)	9 (9.5)	10 (10.6)
Headache	7 (7.3)	5 (5.3)	8 (8.5)
Nasopharyngitis	9 (9.4)	8 (8.4)	8 (8.5)
Dizziness	1 (1.0)	0	6 (6.4)
Acne	1 (1.0)	3 (3.2)	5 (5.3)
Vomiting	0	4 (4.2)	5 (5.3)
Abdominal pain upper	0	0	4 (4.3)
Blood creatine phosphokinase increased	0	4 (4.2)	4 (4.3)
Abdominal pain	1 (1.0)	1 (1.1)	3 (3.2)
Pharyngitis	3 (3.1)	5 (5.3)	3 (3.2)
Sinusitis	0	0	3 (3.2)
Folliculitis	1 (1.0)	7 (7.4)	2 (2.1)
Influenza	1 (1.0)	4 (4.2)	2 (2.1)
Atopic dermatitis	3 (3.1)	2 (2.1)	1 (1.1)
Cough	2 (2.1)	4 (4.2)	1 (1.1)
Pyrexia	4 (4.2)	3 (3.2)	1 (1.1)
Rhinorrhea	3 (3.1)	1 (1.1)	0
TEAEs of special interest			
Herpes zoster	0	1 (1.1)	0
Herpes simplex	0	0	1 (1.1)
Oral herpes	0	1 (1.1)	2 (2.1)
Eczema herpeticum	0	1 (1.1)	0
Conjunctivitis	1 (1.0)	0	0

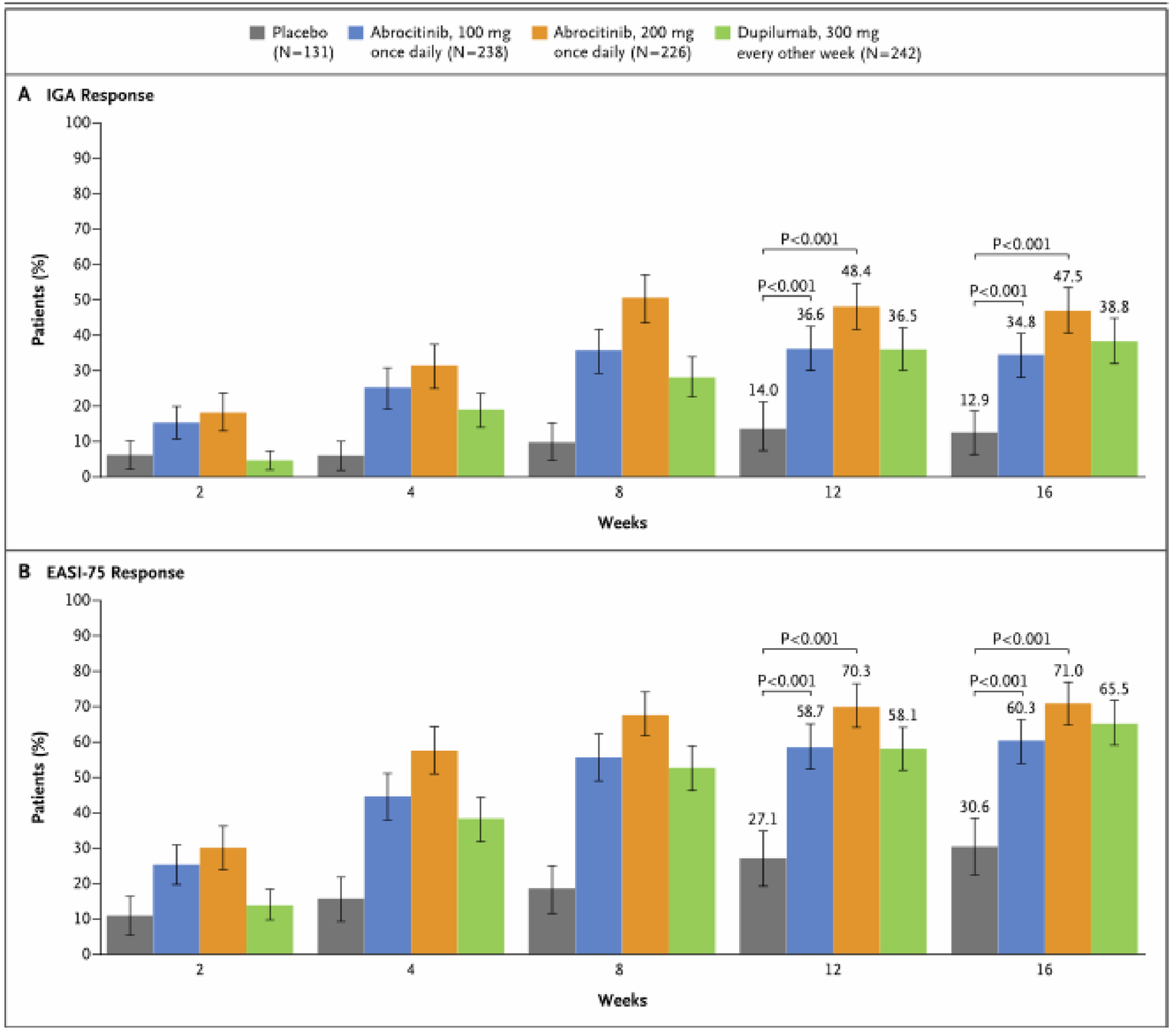


Tabla y gráficas extraídas de Bieber T, et al. N Engl J Med. 2021

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Availability of drugs for children

Price, age and comorbidities as limiting factors

Drug	Age of approval	Remarks
Biologics		
Dupilumab	> 6 months	Prurigo nodularis, Asthma, Nasal polyposis, Eosinophilic esophagitis
Tralokinumab	> 12 years	Ongoing evaluation > 6 months
Lebrikizumab	> 12 years	Ongoing evaluation > 6 months
Nemolizumab	> 12 years	Prurigo nodularis; ongoing evaluation > 2 years
JAK inhibitors		
Baricitinib	> 2 years	Alopecia areata (adults; ongoing evaluation in children)
Abrocitinib	> 12 years	Ongoing evaluation > 2 years
Upadacitinib	> 12 years	Ongoing evaluation > 2 years

Treatment of atopic dermatitis: Recently approved drugs and advanced clinical development programs

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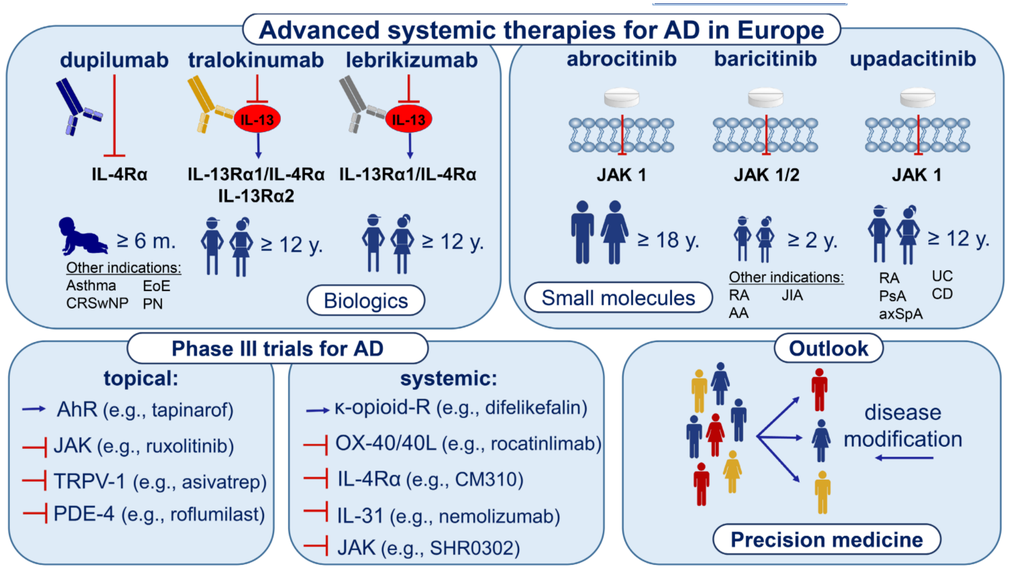
Abstract

Atopic dermatitis (AD) represents the most common skin disease characterized by heterogeneous endophenotypes and a high disease burden. In Europe, six new systemic therapies for AD have been approved: the biologics dupilumab (anti-interleukin-4 receptor (IL-4R) α in 2017), tralokinumab (anti-IL-13 in 2021), lebrikizumab (anti-IL-13 in 2023), and the oral janus kinase (JAK) inhibitors (JAKi) targeting JAK1/2 (baricitinib in 2020 in the EU) or JAK1 (upadacitinib in 2021 and abrocitinib in 2022). Herein, we give an update on new approvals, long-term safety, and efficacy. Upadacitinib and abrocitinib have the highest short-term efficacy among the approved systemic therapies. In responders, dupilumab and tralokinumab catch up regarding long-term efficacy and incremental clinical benefit within continuous use. Recently, the European Medicines Agency has released recommendations for the use of JAKi in patients at risk (cardiovascular and thromboembolic diseases, malignancies, (former) smoking, and age ≥65 years). Furthermore, we give an overview on emerging therapies currently in Phase III trials. Among the topical therapies, tapinarof (aryl hydrocarbon receptor), ruxolitinib (JAK1/2i), delgocitinib (pan-JAKi), asivatrep (anti-transient receptor potential vanilloid), and phosphodiesterase-4-inhibitors (roflumilast, difamilast) are discussed. Among systemic therapies, current data on cord-blood-derived mesenchymal stem cells, CM310 (anti IL-4Rα), nemolizumab (anti-IL-31RA), anti-OX40/



Target	Agent	Approved (+/−) or (clinical trial) AD*	Asthma
Adaptive immune response			
Th2 cytokines and receptors			
IL-4R/IL-13R	Dupilumab	+ (≥6 months)	+ (≥6 years)
IL-13/IL-4	Tralokinumab	+ (≥12 years)	- (III)
IL-13/IL-4	Lebrikizumab	+ (≥12 years)	- (III)
IL-4R	CM310	- (III)	- (II/III)
Immunoglobulin E			
IgE	Omalizumab	- (IV)	+ (≥6 years)
Histamine			
H1-R	Bepotastine besilate	- (III)	-
H1-R	Ketotifen fumarate	- (III)	- (IV)
Antigen presentation			
OX 40	AG 451/KHK 4083	- (III)	-
Microbiome			
Bacteria	Broncho-Vaxom (OM-85 BV)	- (III)	- (IV)
Pruritus			
IL-31	Nemolizumab	+ (Japan: ≥13 years: itch associated with AD, when prior treatment is insufficiently effective) (III)	-
NK1R	Serlopitant	- (III)	-
NK1R	Tradipitant	- (III)	-
κ-opioid-R	Difelikefalin	- (III)	-
Janus kinase inhibitors			
JAK1/JAK2	Baricitinib	+ (≥2 years)	-
JAK1	Upadacitinib	+ (≥12 years)	-
JAK1	Abrocitinib	+ (≥18 years)	-
JAK1	SHR0302	- (III)	-
Pan-JAKi	Jaktinib	- (III)	-
Mesenchymal stem cells (human umbilical cord-blood derived)			
Unknown	FURESTEM	- (III)	-