dermatologieaare

Atopische Dermatitis
Was gibt es Neues?

Obach Privatklinik, 11.11.2021

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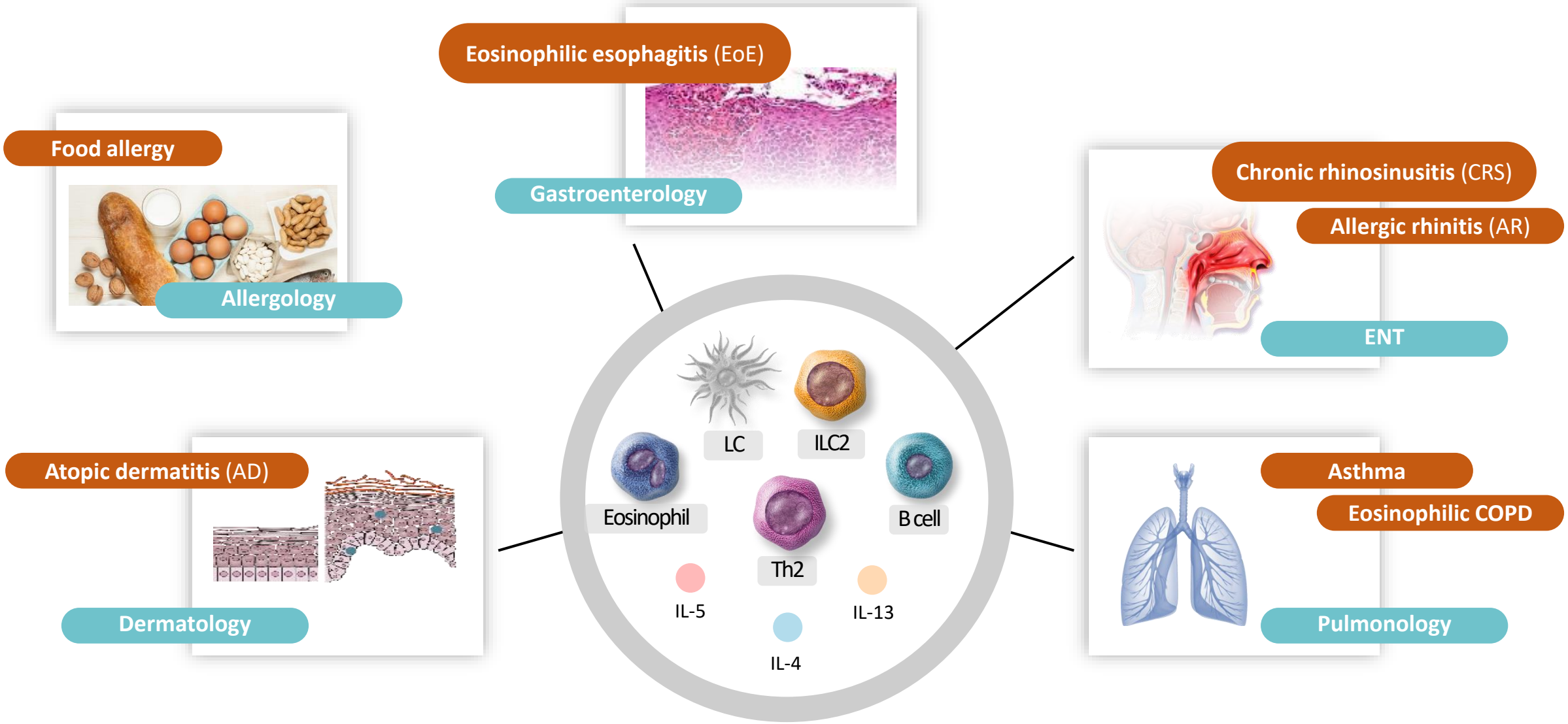


Figure adapted from following references:

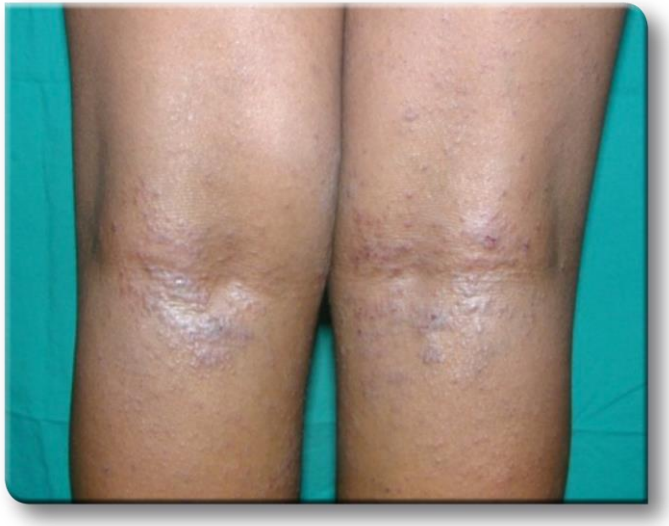
1. Gandhi NA, et al. Targeting key proximal drivers of type 2 inflammation in disease. Nat Rev Drug Discov. 2016;15(1):35-50

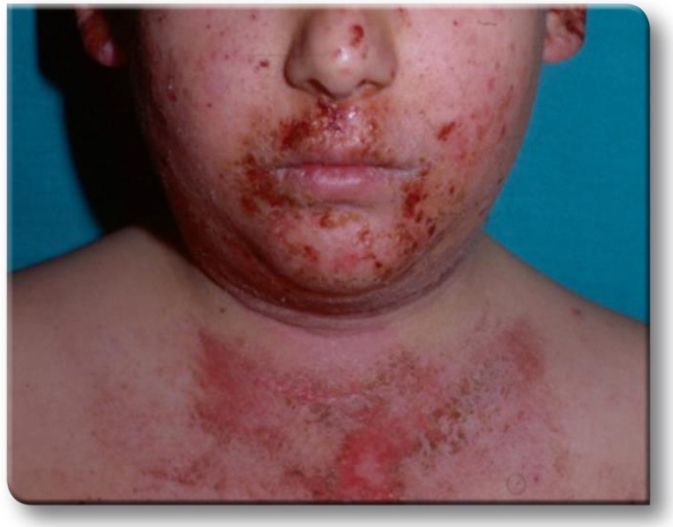
2. Carr S, et al. Eosinophilic esophagitis. Allergy Asthma Clin Immunol. 2011;7(suppl 1):S8;

3. Steinke JW, Wilson JM. Aspirin-exacerbated respiratory disease: pathophysoilogical insights and clinical advances. Asthma Allergy. 2016;9:37-43.

Atopische Dermatitis

- AD eine entzündliche, chronische und stark juckende Hauterkrankung; nicht heilbar.[1-3]
- Typische Lokalisation: Gesicht, Hals, Kopf und in den Beugen.[4]
- Pathophysiologie: Dysfunktion der Hautbarriere und Dysregulation des Immunsystems.[5,6]

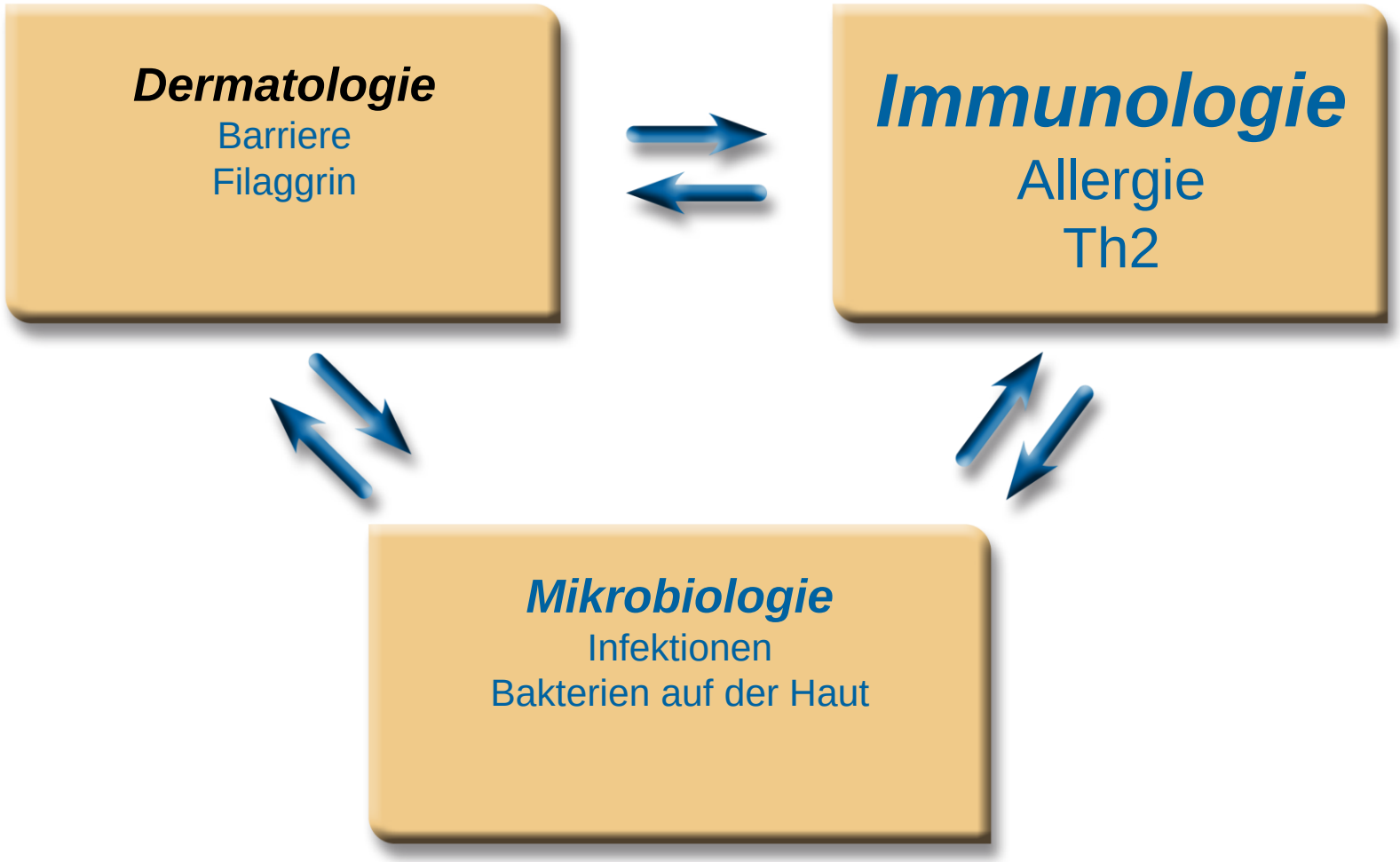




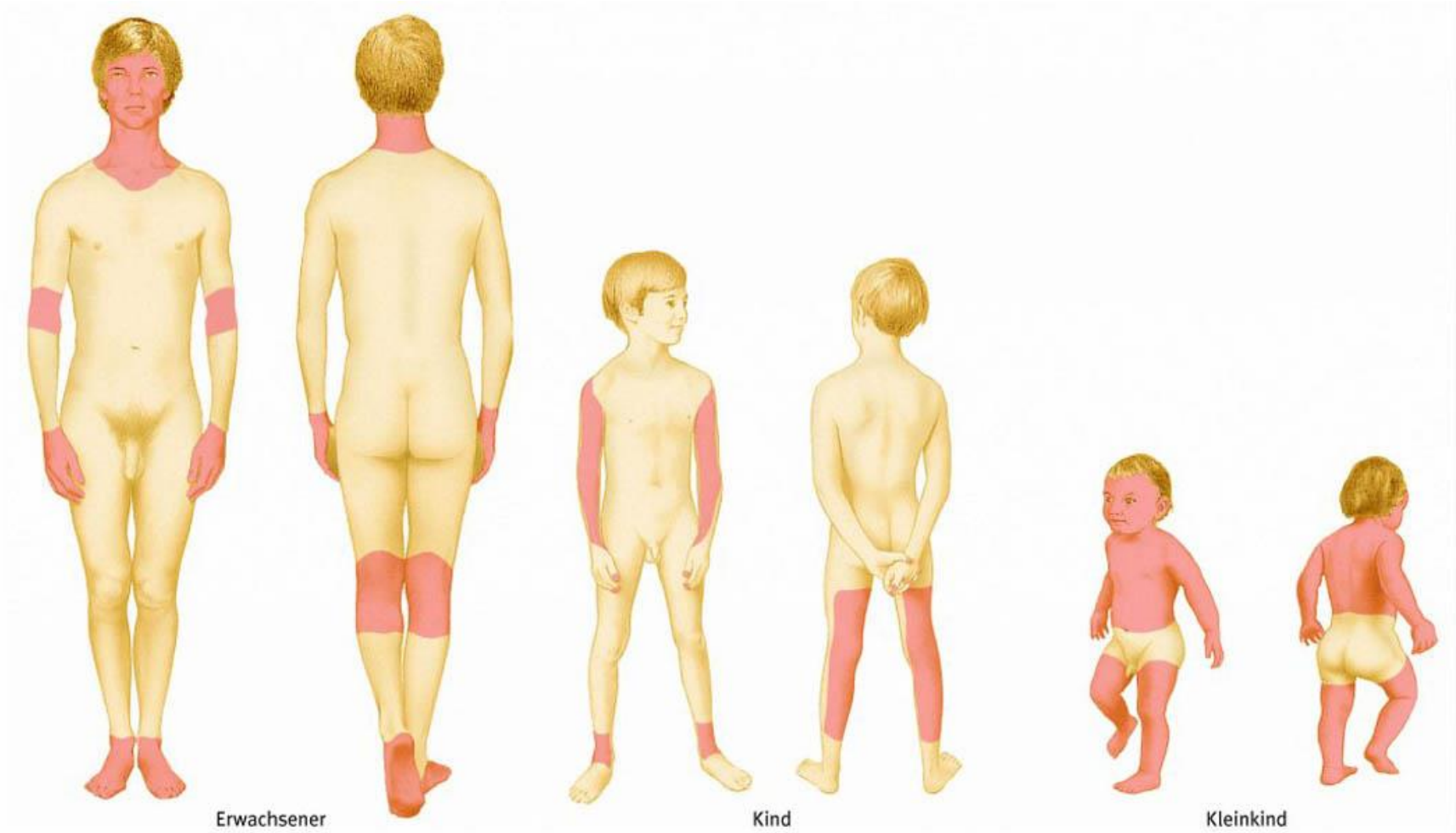
Photos courtesy Dr. Antonio Torrelo

Ref: [1] Darsow U et al. ETFAD/EADV eczema task force 2009 position paper on diagnosis and treatment of atopic dermatitis. J Eur Acad Dermatol Venereol 2010; 24(3):317-328; [2] Ring J et al. Guidelines for treatment of atopic eczema European Dermatology Forum 2012; [3] Akdis CA et al. Diagnosis and treatment of atopic dermatitis in children and adults: European Academy of Allergology and Clinical Immunology/American Academy of Allergy, Asthma and Immunology/PRACTALL Consensus Report. J Allergy Clin Immunol 2006; 118(1):152-169; [4] Hoeger PH et al. J Dermatol 2009; 160(2):-441522; [5] Ellis C et al. Br J Dermatol 2003; 148 Suppl 63:3-10; [6] Werfel T. J Invest Dermatol 2009; 129(8):1878-1891

Pathomechanismus



Atopische Dermatitis (AD)



Behandlungsoptionen[1,2]

- **Emmollentien** (Basistherapie)
- **Topische Behandlung:**
  - Topische Corticosteroide (TCS)
  - Topische Calcineurininhibitoren (TCI):
    - Pimecrolimus 1% Creme (Elidel®)
    - Tacrolimus 0,1% und 0,03% Salbe (Protopic®)
- Juckreizmindernde Therapie
- Antihistaminika
- Antimikrobielle Therapie
- Phototherapie
- Systemische Immunsuppression (orale Glucorticoide, Methotrexat, Ciclosporin A, Azathioprin, Mycophenolat…)
- Biologika
- Allergen-spezifische Immunotherapie (ASIT)

Ref: [1] Plotz SG, Ring J. Expert Opin Emerg Drugs 2010; 15(2):249-267; [2] Ring J et al. Guidelines for treatment of atopic eczema European Dermatology Forum 2012; 1-75

Basistherapie: Reinigung & Emollentien[1-4]

- Sorgfältige Reinigung ist wichtig um Krusten zu entfernen.
- Nicht irritierende und milde Reinigungsmittel mit oder ohne Antiseptika verwenden pH neutral (pH 6).
- Kurze Bäder von max. 10 Minuten, in den letzten 2 Minuten Badeöl als Zusatz, sollen die dermale Dehydratation verhindern.
- Emmollentien gleich nach dem Bad oder Dusche auftragen, wenn die Haut nach dem vorsichtigen Abtrocknen noch feucht ist. Mindestens 2x/Tag auftragen, selbst wenn die Haut normal aussieht.

Ref: [1] Darsow U et al. ETFAD/EADV eczema task force 2009 position paper on diagnosis and treatment of atopic dermatitis. J Eur Acad Dermatol Venereol 2010; 24(3): 317-328; [2] Ring J et al. Guidelines for treatment of atopic eczema European Dermatology Forum 2012; 1-75; [3]Cork MJ et al. Br J Nursing 2009;13:876-877; [4]Grimalt R et al. Dermatol 2007;214:61-6;

Topische Corticosteroide

- TCS werden nach der Wirkstärke eingeteilt[1]:
  - Gruppe I: Mild
  - Gruppe II: Moderat
  - Gruppe III: Stark
  - Gruppe IV: Sehr stark[2]
- **Corticosteroide der Klasse III und IV sollten nicht in Bereichen mit dünner Haut eingesetzt werden –** Augenlider, Gesicht, Schleimhäute, Genitalbereich, Leistengegend (vermehrte Resorption)[2,3].
- Vorteile von TCS – kostengünstige Therapie, verschiedene galenische Formen (Milch, Lotion, Creme, Salben, Fettsalben), und klinische Wirksamkeit seit über 50 Jahren[2].

→ Keine Angst von topischen Steroiden !!!

Ref: [1] Darsow U et al. ETFAD/EADV eczema task force 2009 position paper on diagnosis and treatment of atopic dermatitis. J Eur Acad Dermatol Venereol 2010; 24(3):317-328; [2] Leung DY et al. Ann Allergy Asthma Immunol 2004; 93(3 Suppl 2):S1-21; [3] Peterson JD et al. Dermatol Nurs 2006; 18(6):531-54

Topische Calcineurin Inhibitoren

- **„Second-line“ Therapie**
- **TCIs verhindern durch Hemmung des Enzyms Calcineurin, die T-Zell-Aktivierung und die Ausschüttung von pro-inflammatorischen Zytokinen aus den aktivierten T-Zellen**[1].
- TCIs führen zu **keiner Hautatrophie** [2-5].
- TCIs sind den TCS überlegen:
  - In sensiblen Arealen – Lider, perioral, Genitalbereich, Leistengegend und Achselregion
  - In der Langzeit-Behandlung[2].
- **Empfohlen in sensiblen Hautarealen:** Anwenden bei den ersten Anzeichen der leichten bis mittelschweren AD bei Kindern und Erwachsenen[1,2].
- Klinische und präklinische Daten: **Kein Anzeichen für Lymphom-Risiko oder Photokarzinogenität während eines Beobachtungszeitraumes von 6 Jahren[3,4].**

Ref: [1] Ingram JR et al. Am J Clin Dermatol 2009; 10(4):229-237; [2] Darsow U et al. ETFAD/EADV eczema task force 2009 position paper on diagnosis and treatment of atopic dermatitis. J Eur Acad Dermatol Venereol 2010; 24(3):317-328; [3] Aschoff R et al. Exp Dermatol 2011; 20(10):832-836; [4] Jensen JM et al. J Allergy Clin Immunol 2009; 124(3 Suppl 2):R19-R28; [5] Queille-Roussel C et al. Br J Dermatol 2001; 144(3):507-513

Therapieschema

Möglichst einfach!!!

So

Andere Behandlungmöglichkeiten[1-2]

- Systemische Antihistamingabe häufig im akuten Schub – Juckreizminderung; es gibt aber nur wenige kontrollierte Studien darüber.
- Antibakterielle Therapie: Kombinationspräparate!
  - Topische Formen sollten nur kurzzeitig zur Behandlung der AD angewendet werden
  - Anwendung nur wenn Schub auch mit klinischen Zeichen einer bakteriellen Infektion einhergeht – z. B. nässendes Ekzem, Eiterbildung, Pusteln
- Virale Hautinfektionen treten bei AD Patienten häufiger auf, als in der Normalbevölkerung .
- Bei Auftreten einer viralen Hautinfektion – keine antiinflammatorische Therapie, sondern antivirale Therapie; z.B. könnte sich sonst eine Herpes simplex Infektion zu einem Ekzema herpeticum entwickeln.

Ref: [1] Darsow U et al. ETFAD/EADV eczema task force 2009 position paper on diagnosis and treatment of atopic dermatitis. J Eur Acad Dermatol Venereol 2010; 24(3):317-328;
[2] Ring J et al. Guidelines for treatment of atopic eczema European Dermatology Forum 2012; 1-75

Atopische Dermatitis

Klassische systemische Therapien

- Offiziell nur Cyclosporin
- MTX, Azathioprin (off label)

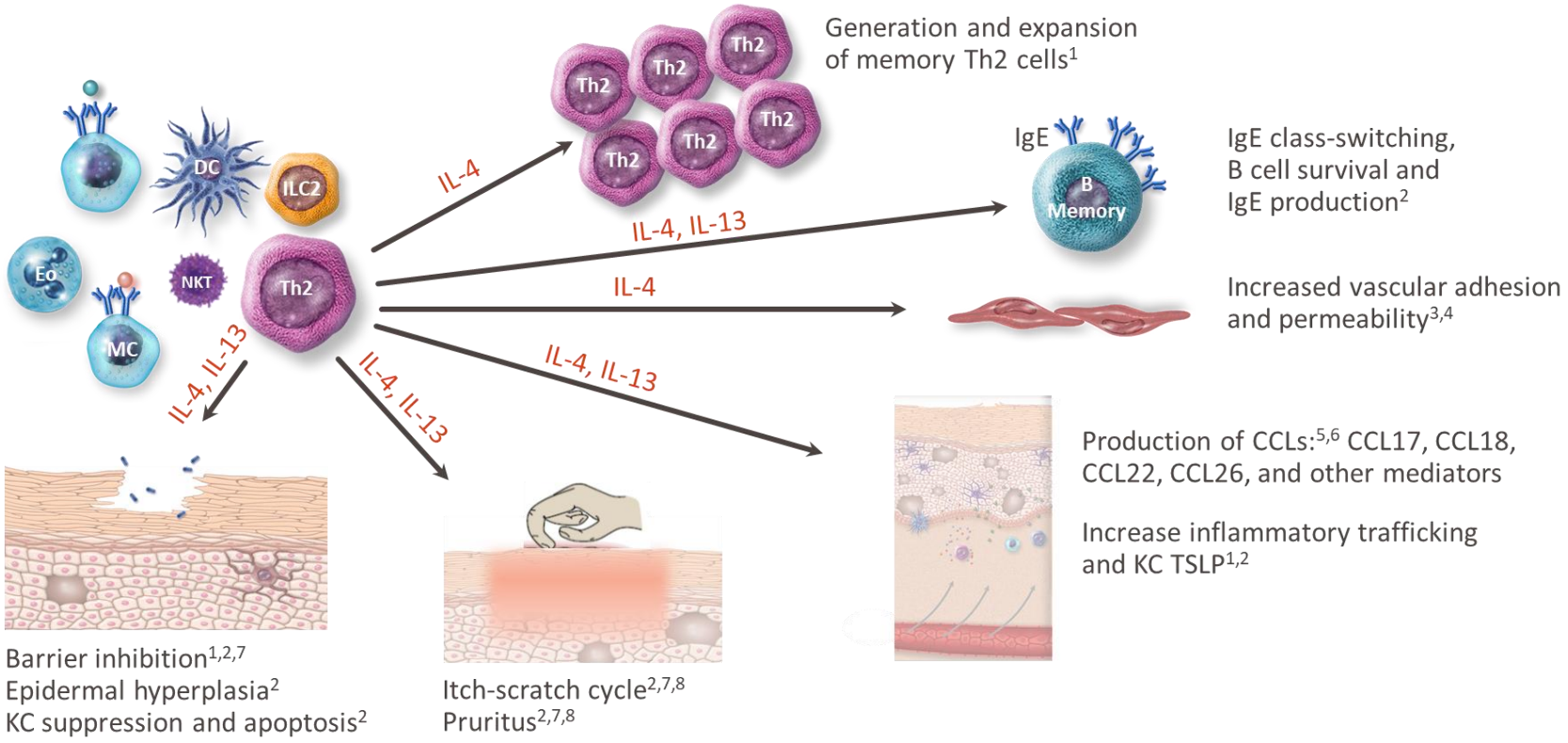
Moderne NEUE systemische Therapien

- IL-4 Blocker: Dupilumab (Dupixent®)
    - 300mg s.c. alle 2 Wo
    - Ca. 15’000CHF/Jahr
    - Keine Vorabklärungen nötig

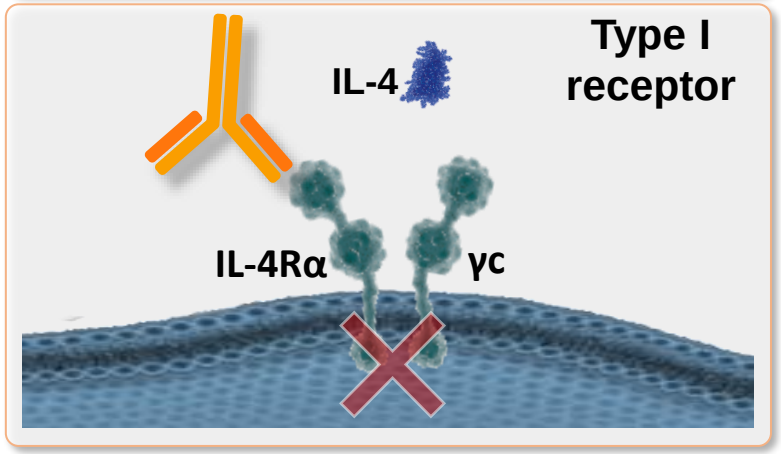
- JAK-Inhibitoren
    - Baricitinib (Olumiant®)
        - 2mg oder 4mg Tbl 1-0-0
        - Ca. 13’000CHF/Jahr
        - Vorabklärungen nötig
    - Upadacitinib (Rinvoq®)

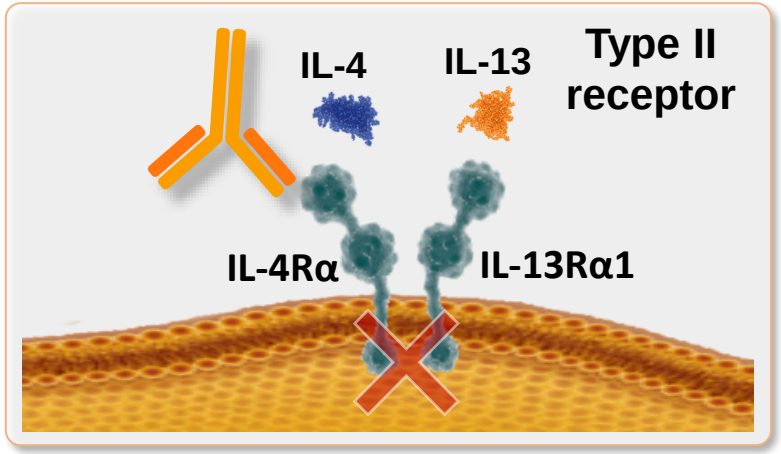
Limitationen

Why Targeting Type 2 Inflammation in AD with Dupilumab?



Dupilumab blocks IL-4Rα, inhibiting the signaling pathways of **both IL-4 and IL-13**[9]

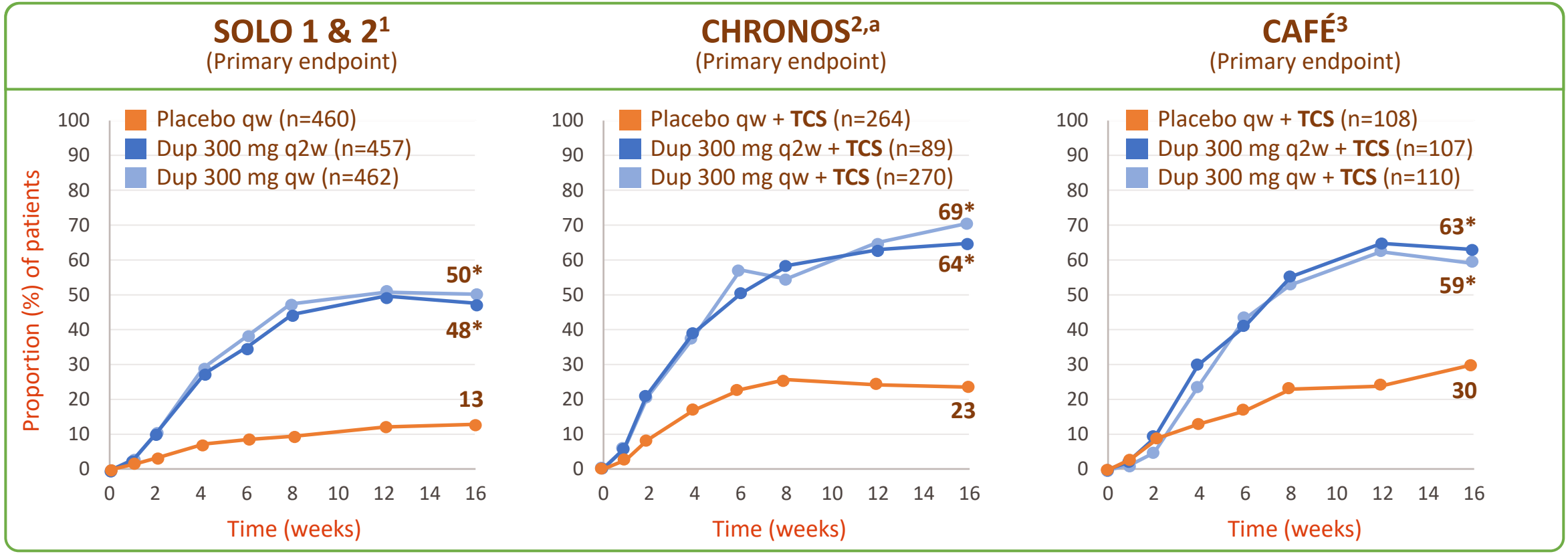




CCL, C-C Motif Chemokine Ligand; DC, dendritic cell; Eo, Eosinophil; IL, Interleukin; ILC2, innate lymphoid cell 2; KC, keratinocyte; MC, mast cell; NKT, natural killer T cell; TSLP, Thymic stromal lymphopoietin.

1. Palomares O, et al. Mechanisms of immune regulation in allergic diseases: the role of regulatory T and B cells Immunol Rev. 2017;278(1):219-236. 2. Weidinger S, et al. Atopic dermatitis Nat Rev Dis Primers. 2018;4:1. 3. Patel D, et al. Eosinophil tethering to interleukin-4-activated endothelial cells requires both P-selectin and vascular cell adhesion molecule-1 Blood. 1998; 98:3904-11. 4. Chen, et al. VCAM-1 blockade delays disease onset, reduces disease severity and inflammatory cells in an atopic dermatitis model. Immunol Cell Biol. 2010;88:334-42. 5. Brunner PM, et al. The immunology of atopic dermatitis and its reversibility with broad-spectrum and targeted therapies. J Allergy Clin Immunol. 2017;139(4S):S65-S76. 6. Brandt EB, Sivaprasad U. Th2 Cytokines and Atopic Dermatitis. J Clin Cell Immunol. 2011;2(3). 7. Rerknimitr P, et al. The etiopathogenesis of atopic dermatitis: barrier disruption, immunological derangement, and pruritus. Inflamm Regen. 2017;37:14. 8. Oetjen LK, et al. Sensory Neurons Co-opt Classical Immune Signaling Pathways to Mediate Chronic Itch. Cell. 2017;171:217-228.e13. 9. Gandhi NA, et al. Targeting key proximal drivers of type 2 inflammation in disease; Nat Rev Drug Discov. 2016;15:35-50.

Phase 3 studies through 16 weeks: Consistent EASI-75 response



The only licensed dose for dupilumab in moderate-to-severe AD patients (≥ 18 years) in CH is 300 mg q2w.

- *P<0.0001 vs placebo or placebo + TCS. [a]Presented data are from the FAS-52 of patients who completed the study before the data cutoff. Week 16 statistics use the FAS. Patients who used rescue therapy or withdrew from the trial were classified as non-responders in the statistical analysis.
- Dup=dupilumab; EASI-75=75% improvement in Eczema Area and Severity Index score; FAS=full analysis set; FAS-52=patients in the full analysis set who had completed 52 weeks of treatment and were evaluated for efficacy outcomes by the cutoff date for US Food and Drug Administration submission; q2w=every 2 weeks; qw=weekly; TCS=topical corticosteroids.
- *Figures adapted from the following references: 1. Thaci D et al. Efficacy and safety of dupilumab monotherapy in adults with moderate-to-severe atopic dermatitis: a pooled analysis of two phase 3 randomized trials (LIBERTY AD SOLO 1 and LIBERTY AD SOLO 2). J Dermatol Sci. 2019 May;94(2):266-275. 2. Blauvelt A, et al. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial, Lancet. 2017;389(10086):2287-2303. 3. de Bruin-Weller M, et al. Dupilumab with concomitant topical corticosteroid treatment in adults with atopic dermatitis with an inadequate response or intolerance to ciclosporin A or when this treatment is medically inadvisable: a placebo-controlled, randomized phase III clinical trial (LIBERTY AD CAFÉ), Br J Dermatol. 2018 May;178(5):1083-1101.*

OLE: Sustained safety for up to 3 Years

AE reported by ≥5% of patients (PT)	OLE (through 148 weeks)		CHRONOS (through 52 weeks)			
	Dupilumab 300 mg qw (N=2677)		Placebo + TCS (n=315)		Dupilumab 300 mg qw + TCS (n=315)	
	n (%)	nP/100 pt-y	n (%)	nP/100 pt-y	n (%)	nP/100 pt-y
Nasopharyngitis	752 (28.1)	19.16	62 (19.7)	24.93	62 (19.7)	24.16
Conjunctivitis[a]	**521 (19.5)**	**11.96**	**25 (7.9)**	**9.24**	**61 (19.4)**	**23.37**
Atopic dermatitis	438 (16.4)	9.61	147 (46.7)	74.32	55 (17.5)	20.71
URTI	350 (13.1)	7.56	32 (10.2)	12.03	43 (13.7)	15.85
Herpes viral infection	333 (12.4)	7.21	25 (7.9)	9.71	22 (7.0)	7.72
Injection site reaction	**260 (9.7)**	**5.58**	**25 (7.9)**	**9.39**	**63 (20.0)**	**25.46**
Skin infections	**231 (8.6)**	**4.81**	**57 (18.1)**	**20.21**	**26 (8.3)**	**7.87**
Headache	216 (8.1)	4.54	19 (6.0)	6.98	25 (7.9)	8.97

[a]Includes the following MedDRA preferred terms: conjunctivitis, allergic conjunctivitis, bacterial conjunctivitis, viral conjunctivitis, and atopic keratoconjunctivitis
PT, MedDRA preferred term; nP/100 pt-y, number of patients with events per 100 patient-years

No new safety signals

Most conjunctivitis cases were mild to moderate; 1.0% of patients reported severe conjunctivitis

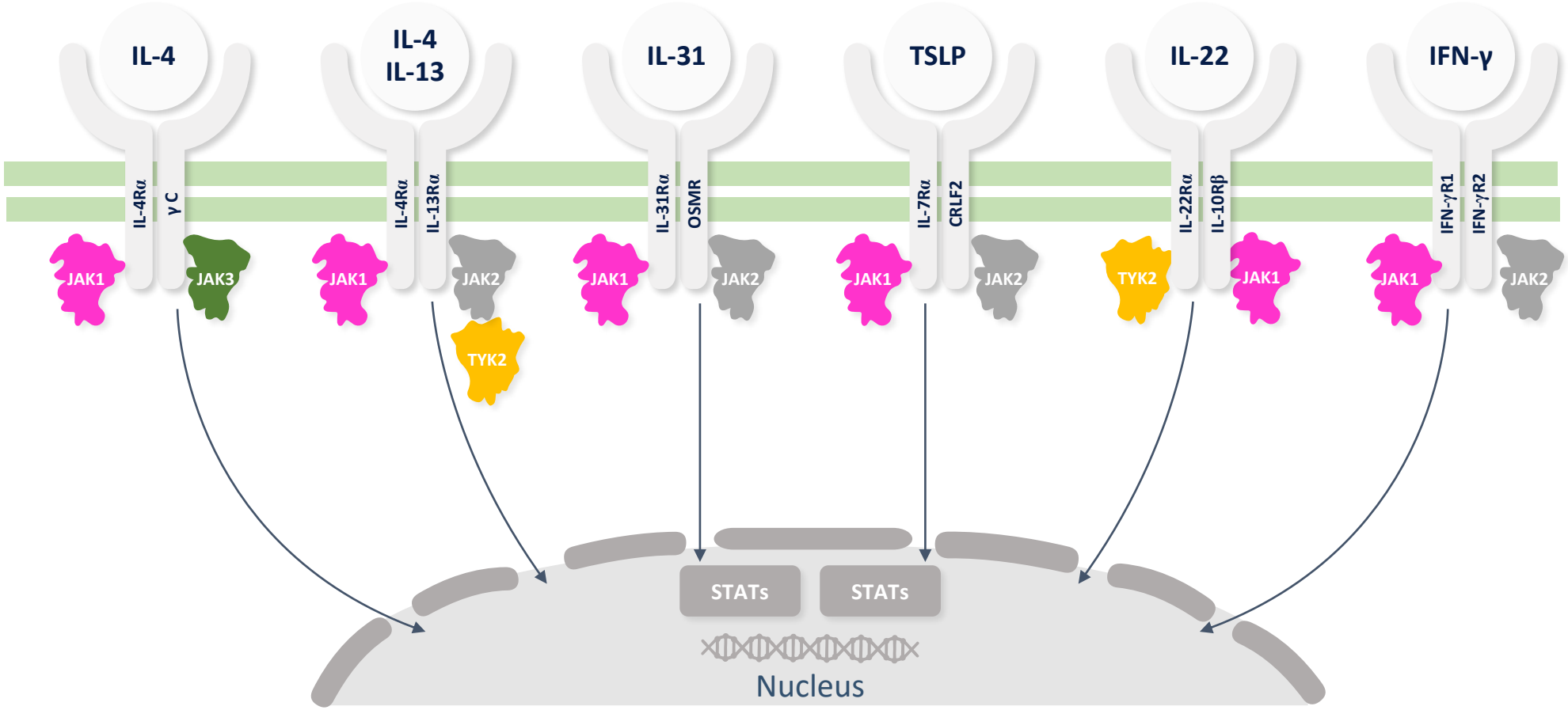
0.5% permanently discontinued due to Conjunctivitis

Rate of treatment discontinuation due to AEs was low (3.5%) and self-reported compliance with study treatment was high (98%)

Figure adapted from Beck LA, Thaçi D, Deleuran M, et al. Dupilumab Provides Favorable Safety and Sustained Efficacy for up to 3 Years in an Open-Label Study of Adults with Moderate-to-Severe Atopic Dermatitis. Am J Clin Dermatol. 2020;21(4):567-577. doi:10.1007/s40257-020-00527-x

The only licensed dose for dupilumab in moderate-to-severe AD patients (≥18 years) in CH is 300 mg q2w.

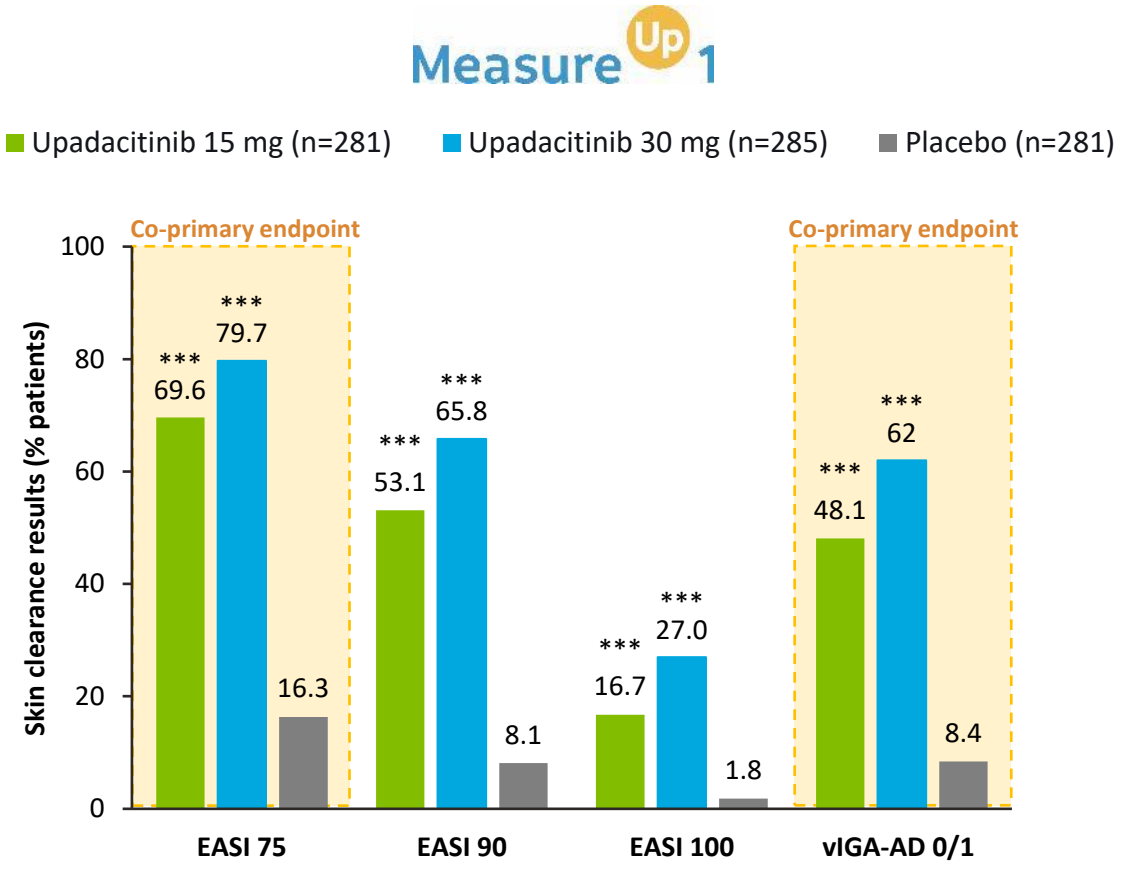
Key cytokines involved in the pathogenesis of atopic dermatitis signal via JAK1

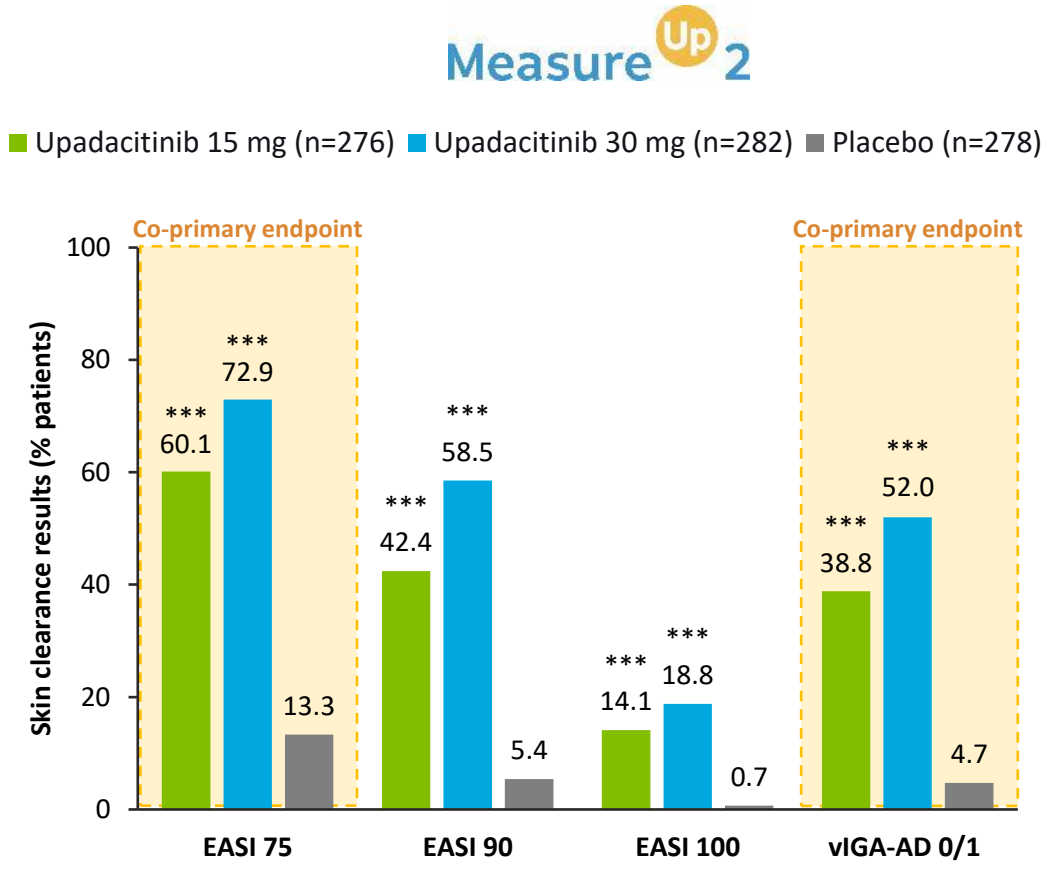


- AD, atopic dermatitis; CRLF2, cytokine receptor like factor 2; IFN, interferon; IL, interleukin; JAK, Janus kinase; OSMR, oncostatin M receptor; STAT, signal transducers and activators of transcription; TSLP, thymic stromal lymphopoietin; TYK2, tyrosine kinase 2

Virtanen A, et al. *BioDrugs* 2019;33:15–32; Cornelissen C, et al. *Eur J Cell Bio* 2012:552–66;
Castro F, et al. *Front Imm* 2018:9:847; Keegan AD, et al. *Front Imm* 2018:9:1037

Phase 3 upadacitinib monotherapy studies: skin clearance EASI 75, 90, 100 and vIGA-AD 0/1 at Week 16[1]





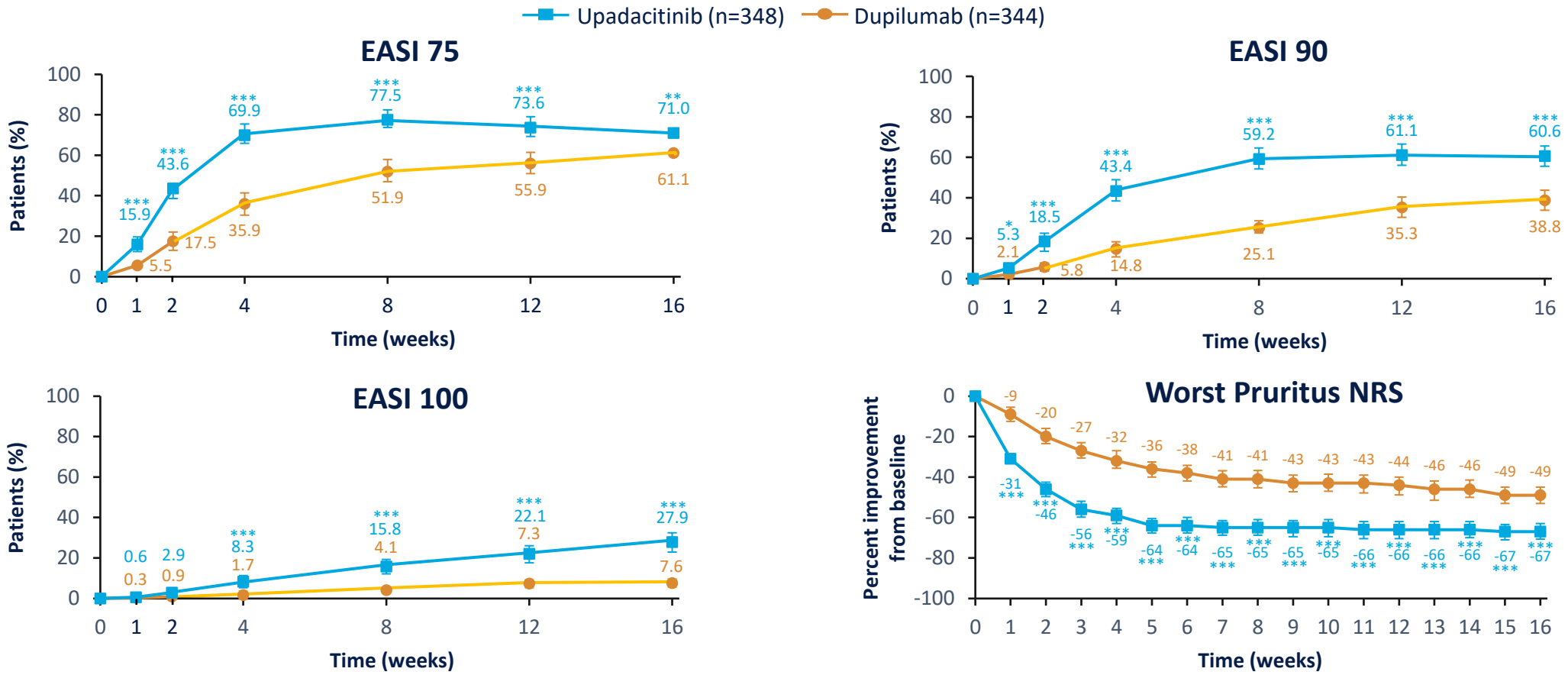
Graphs adapted from Guttman-Yassky E, et al. [1]

EASI 75 at Week 16: 60–70% (15 mg) and 73–80% (30 mg) (*P*<0.001 vs placebo)

- Based on ITT Population, NRI-C.
  Missing due to COVID-19 which were imputed by MI: 7 in Measure Up 1, 5 in Measure Up 2.
  ***P<0.001 vs placebo (multiplicity controlled)
- COVID-19, coronavirus disease 2019; EASI 75/90/100, proportion of patients achieving ≥75/90/100% reduction in Eczema Area and Severity Index; ITT, intent-to-treat for the main study; MI, multiple imputation; NRI-C, non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19; vIGA-AD 0/1, proportion of patients achieving validated Investigator's Global Assessment for Atopic Dermatitis of clear (0) or almost clear (1) with ≥2 grades of reduction from baseline

1. Guttman-Yassky E, et al. Oral presentation at EADV 2020, D3T03.4B

Upadacitinib Phase 3b efficacy: EASI 75/90/100 and Worst Pruritus NRS over time[a]



Upadacitinib met the primary endpoint and all key secondary endpoints vs dupilumab in the Heads Up study

- *p≤0.05; **p≤0.01; ***p≤0.001; error bars indicate 95% confidence interval
  [a]Percent improvement in Worst Pruritus NRS from baseline vs dupilumab at Weeks 1, 4, and 16 were ranked secondary endpoints, as were EASI 90, EASI 100, and proportion of subjects achieving ≥4-point improvement in Worst Pruritus NRS from baseline at Week 16
  DUPI, dupilumab; EASI 75/90/100, ≥75%/90%/100% reduction in Eczema Area and Severity Index; EOW, every other week; NRS, numeric rating scale

Blauvelt A, et al. ISAD 2021 (PT-29)

Integrated safety analysis out to 16 weeks: TEAEs

Overall TEAEs, n (%)	UPA 15 mg (n=899)	UPA 30 mg (n=906)	PBO (n=902)
All TEAEs	574 (63.8)	630 (69.5)	528 (58.5)
AE with reasonable possibility of being drug-related	298 (33.1)	367 (40.5)	185 (20.5)
Severe AEs	43 (4.8)	42 (4.6)	43 (4.8)
Serious AEs	19 (2.1)	19 (2.1)	26 (2.9)
AEs leading to discontinuation	21 (2.3)	26 (2.9)	34 (3.8)
Death	0	0	0
Most commonly reported AEs[a], n (%)			
Acne	86 (9.6)	137 (15.1)	20 (2.2)
Nasopharyngitis	79 (8.8)	94 (10.4)	64 (7.1)
Upper respiratory tract infection	70 (7.8)	83 (9.2)	58 (6.4)
Headache	50 (5.6)	57 (6.3)	39 (4.3)
CPK elevation	41 (4.6)	50 (5.5)	21 (2.3)
Oral herpes	23 (2.6)	47 (5.2)	9 (1.0)
Dermatitis atopic	31 (3.4)	14 (1.5)	74 (8.2)

- Similar rates of serious AEs and AEs leading to discontinuation were observed across treatment groups
- Most acne events were mild or moderate (1 severe event), none were serious, and 2 led to treatment discontinuation
- Most acne involved the face and consisted primarily of inflammatory papules, pustules, and comedones

- [a]AEs reported for ≥5% of patients in any treatment group
  AE, adverse event; CPK, creatine phosphokinase; PBO, placebo; TEAE, treatment-emergent adverse event; UPA, upadacitinib

- Guttman-Yassky E, et al. AAD 2021 (27082)

Fazit

- Lokale Therapie: immer noch am wichtigsten
  - Muss aber korrekt durchgeführt werden und Pat. instruiert werden
- Neue Systemtherapien
  - Für schwere Fälle reserviert
  - Limitationen/Kosten

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