Systemic treatment and therapeutic pipeline for atopic dermatitis

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When to start systemic treatment for AD? (JAAD 2017;77:623-33)

- Physicians should **optimize topical therapy** before considering systemic medications for atopic dermatitis.
- Patients who fail to respond should be evaluated for exacerbating factors such as **cutaneous infection** and for alternative diagnoses such as **allergic contact dermatitis.**
- The decision to start systemic therapy depends on **disease severity**, **impact on quality of life**, and **risks and benefits** of systemic therapies for the individual patient.

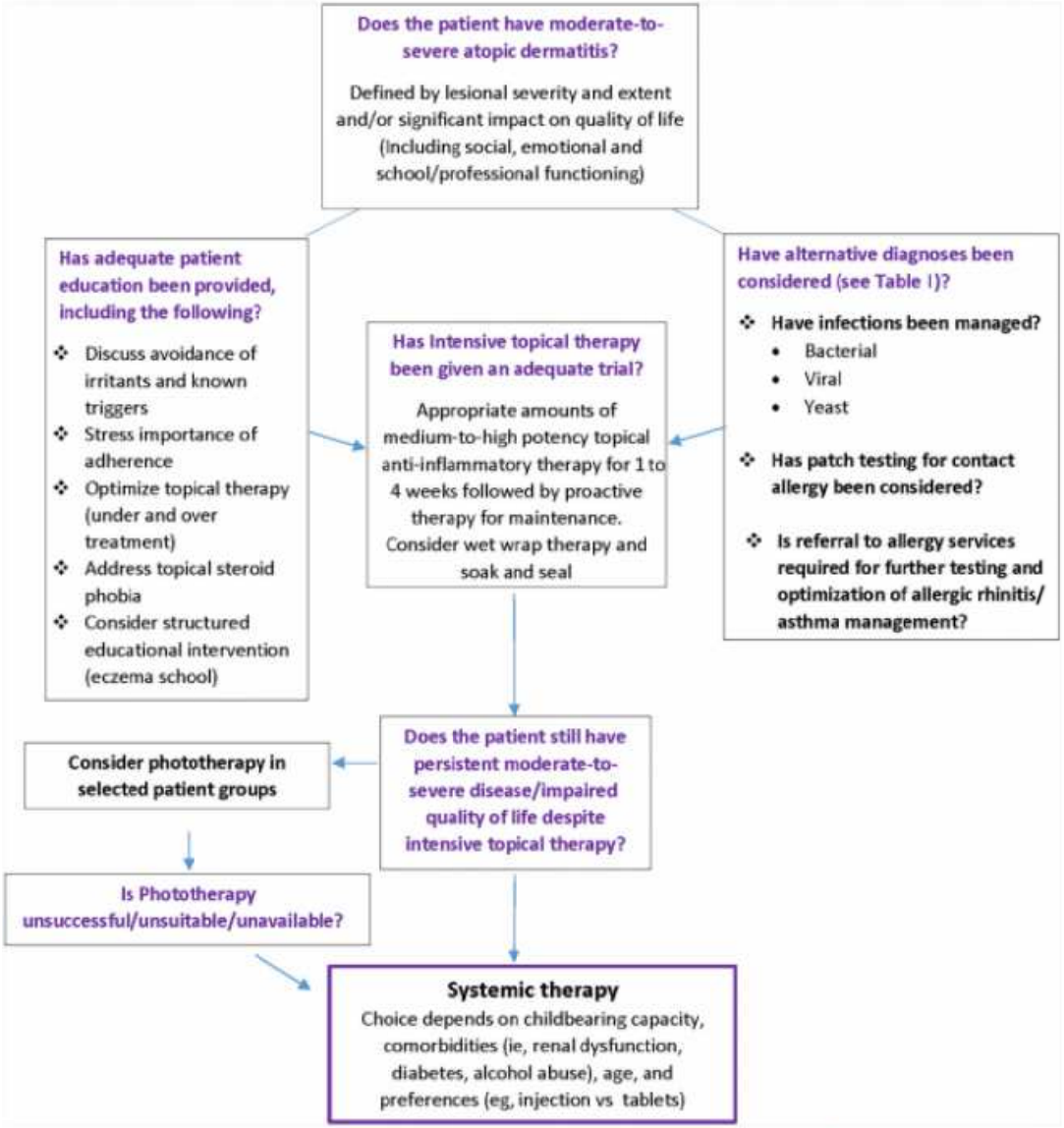


Fig 1. Algorithm to decide when systemic immunomodulatory therapy is warranted in patients with atopic dermatitis.

JAAD 2017;77:623-33

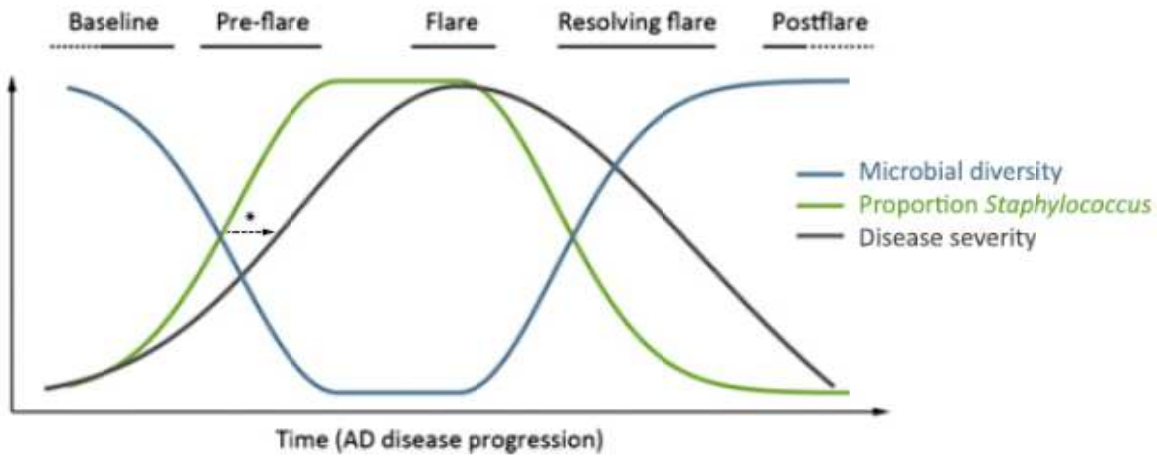
Systemic treatment for AD

- Anti-infectious treatments
- Immunosuppressive treatments
  - Corticosteroïds
  - Cyclosporine A
  - Azathioprine
  - Mycophenolate mofetil
  - Methotrexate

- Biologics
- JAK inhibitoren

Systemic treatment for AD: anti-infectious treatment

- Antibacterial
  - 90% of AD patients are colonized with S. aureus
  - Elicits AD flares
  - Disrupted microbiome plays a role in pathofysiology

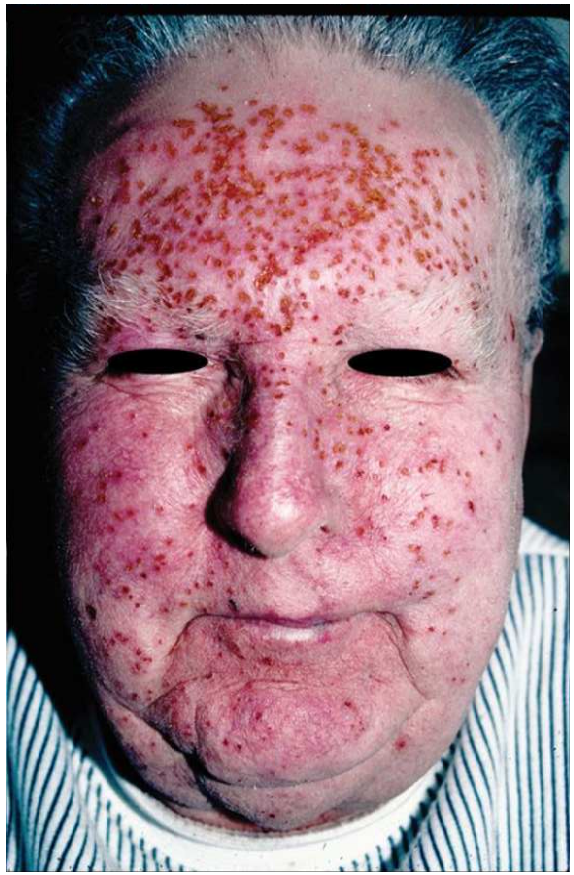


Systemic treatment for AD: anti-infectious treatment

- Antibacterial
  - Treatment
    - Local or systemic antibiotics only in case of flares
    - Anti-septics (eg bleach baths) in case of frequent bacterial infections

Systemic treatment for AD: anti-infectious treatment

- Antiviral
  - Treatment:
    - Disseminated herpes simplex infections: eczema herpeticum
    - Urgent treatment with aciclovir

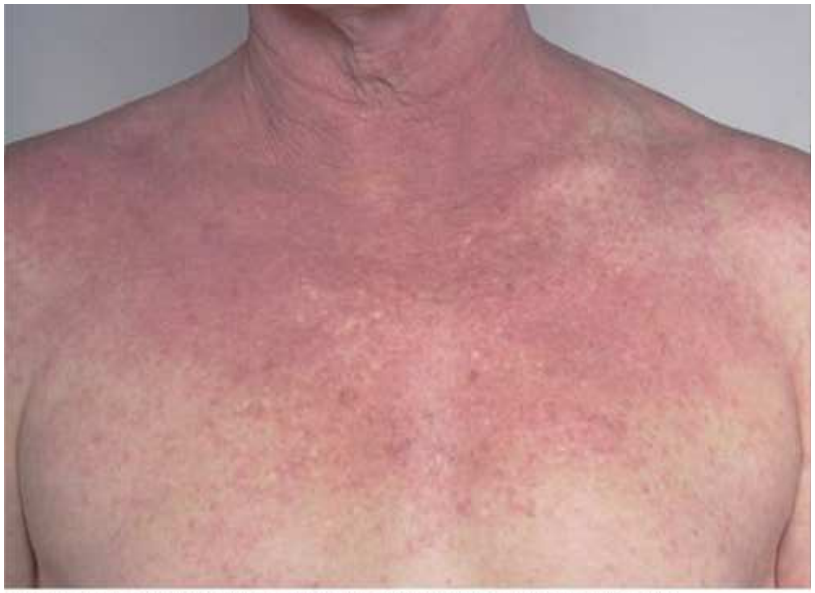


Semin Plast Surg. 2016 Aug; 30(3): 98–107.

Systemic treatment for AD: anti-infectious treatment

- Antifungal
  - Anti-fungal treatment:
    - Malassezia spp plays a role in immune respons and barrier function
    - Treatment is usefull in case of:
      - Head and neck dermatitis
      - IgE directed to malassezia

  - Itraconazole 100 mg/day for 1 week (introduction phase) then 200 mg/week (maintenance phase) for 11 weeks.



Systemic treatment for AD: anti-inflammatory treatment

- Systemic “broad-acting” immunosuppressants (J Allergy Clin Immunol 2014 Feb;133(2):429-38)
  - Cyclosporin (1st line, up to 1 yr)
  - Azathioprin
  - Methotrexate
  - Mycophenolate mofetil
  - Short course systemic corticosteroids

Table II. Most common on-label and off-label systemic therapies in AD

Drug (in alphabetical order)	Approved for AD?	Estimated efficacy (% reduction in composite severity scores)	Dose range	Common or serious side effects	Monitoring required*
Azathioprine	No	26%-39%[5]	Adult: 1-3 mg/kg/day; Pediatric: 1-4 mg/kg/day	Hematologic abnormalities, skin and other malignancies, hepatosplenic lymphoma, and CNS infections such as PML	CBC, CMP, thiopurine methyltransferase
Cyclosporine	No in United States, yes in Europe	53%-95%[5]	Adult and pediatric: 2.5-5 mg/kg	Renal insufficiency, hypertension, and drug interactions	CBC, CMP, magnesium, uric acid, lipids, and blood pressure
Dupilumab	Yes	73%[8,12]	Adult: 600 mg loading followed by 300 mg/wk	Injection site reactions and conjunctivitis	None
Methotrexate	No	42%[5]	Adult: 7.5-25 mg weekly Pediatrics: 0.2-0.7 mg/kg weekly	Hepatoxicity, hematologic abnormalities, teratogen, gastrointestinal intolerance, nausea, and fatigue	CBC, CMP
Mycophenolate	No	Unknown	1.0-1.5 g orally twice daily Pediatric: 30-50 mg/kg daily	Gastrointestinal, teratogen	CBC, CMP

AD, Atopic dermatitis; *CBC*, complete blood count with differential and platelets; *CMP*, complete metabolic panel with basic chemistries and liver function tests; *CNS*, central nervous system; *PML*, progressive multifocal leukoencephalopathy.
*See published review by Sidbury et al[7] for more complete and detailed information regarding dosing and drug monitoring.

Systemic treatment for AD: anti-inflammatory treatment

- Orale corticosteroids
  - Only short periods, in case of “emergency”

- Cyclosporin A (Neoral ®)
  - First choice in severe eczema where systemic treatment is necessary
  - Rapid improvement, rapid relapse when stopped
  - Dose 5 mg/kg and taper according to clinic
  - Periods of 3-6 months, max 1-2 years
  - Side effects:
    - High blood pressure, impaired kidney function

Systemic treatment for AD: anti-inflammatory treatment

- Azathioprine (Imuran ®)
  - Effectivity demonstrated in clinical trials
  - Side effects: decline in white blood cells, liver function, gastro-intestinal symptoms
- Mycophenolate mofetil (Myfenax, Cellcept®)
  - Efficacy is comparable to cyclosporine
- Methotrexate (Ledertrexate ®)
  - Efficacy comparable to azathioprine, cyclosporine
  - Decline in white blood cells, liver function, gastro-intestinal symptoms

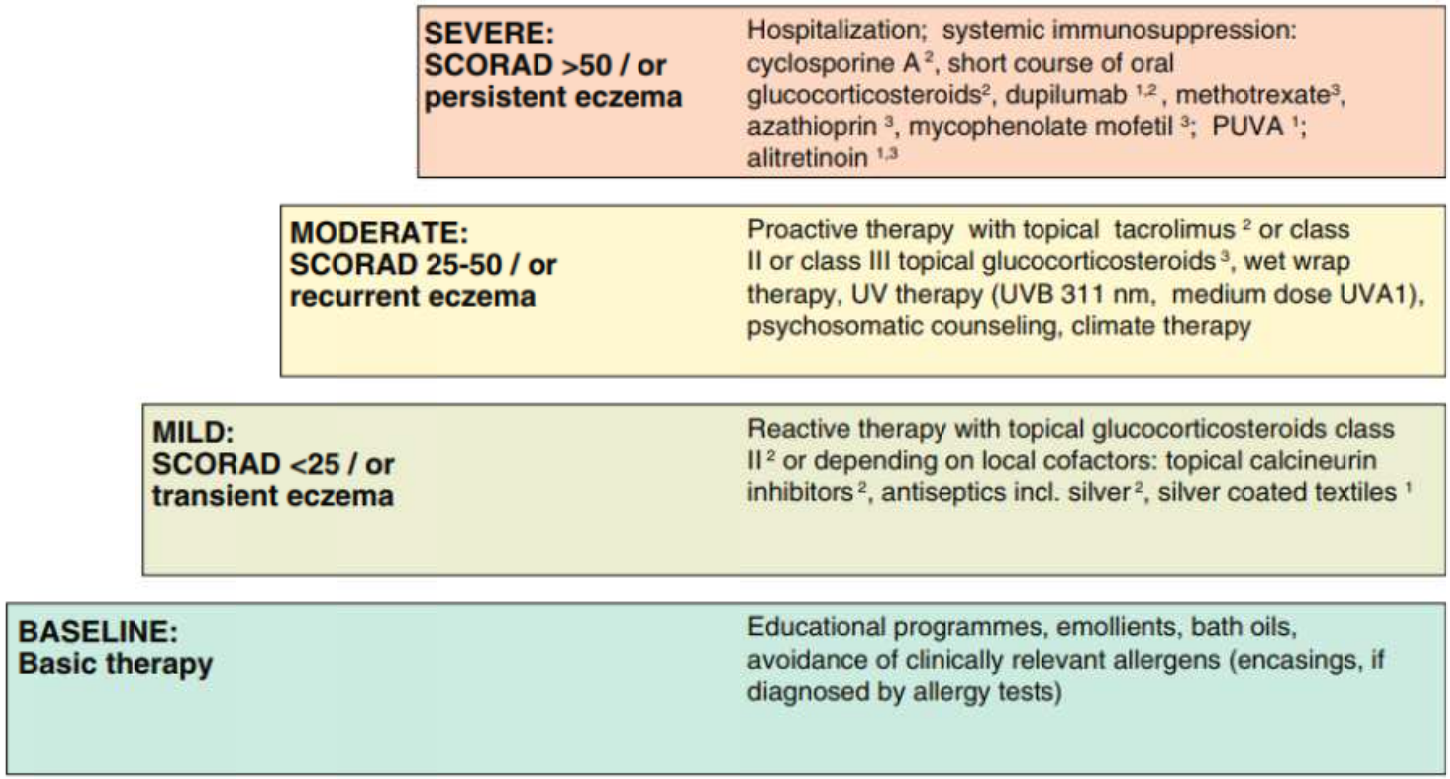
Systemic treatment for AD: anti-inflammatory treatment

Table 4 Systemic drugs for treatment of severe atopic eczema

	Cyclosporine	Methotrexate	Azathioprine	Mycophenolic acid	Corticosteroids
Overall recommendation	++ acute flare intervention	++ long-term maintenance	Can be used long term	++ little toxicity	Outdated‡
Time to respond (weeks)§	2	8–12	8–12	8–12	1–2
Time to relapse (weeks)	<2	>12	>12	>12	<2
Most important side-effects	Serum creatinine ↑ blood pressure ↑	Haematological liver enzymes ↑ gastrointestinal	Haematological liver enzymes ↑ gastro-intestinal	Haematological skin infections gastro-intestinal	Cushing's osteoporosis diabetes
Starting dose adult	4–5 mg/kg/day‡	5–15 mg/week	50 mg/day‡	MMF 1–2 g/day (EC-MPA 1.44 g/day)	0.2–0.5 mg/kg/day
Maintenance dose adult	2.5–3 mg/kg/day	Most often 15/week; can increase to max 25 mg/week	2–3 mg/kg/day†	MMF 2–3 g/day (EC-MPA 1.44 g/day)	Not for maintenance‡

The current guidelines adults

(Wollenberg A et al, JEADV 2018; 32: 850-878)



The current guidelines children

(Wollenberg A et al, JEADV 2018; 32: 850-878)

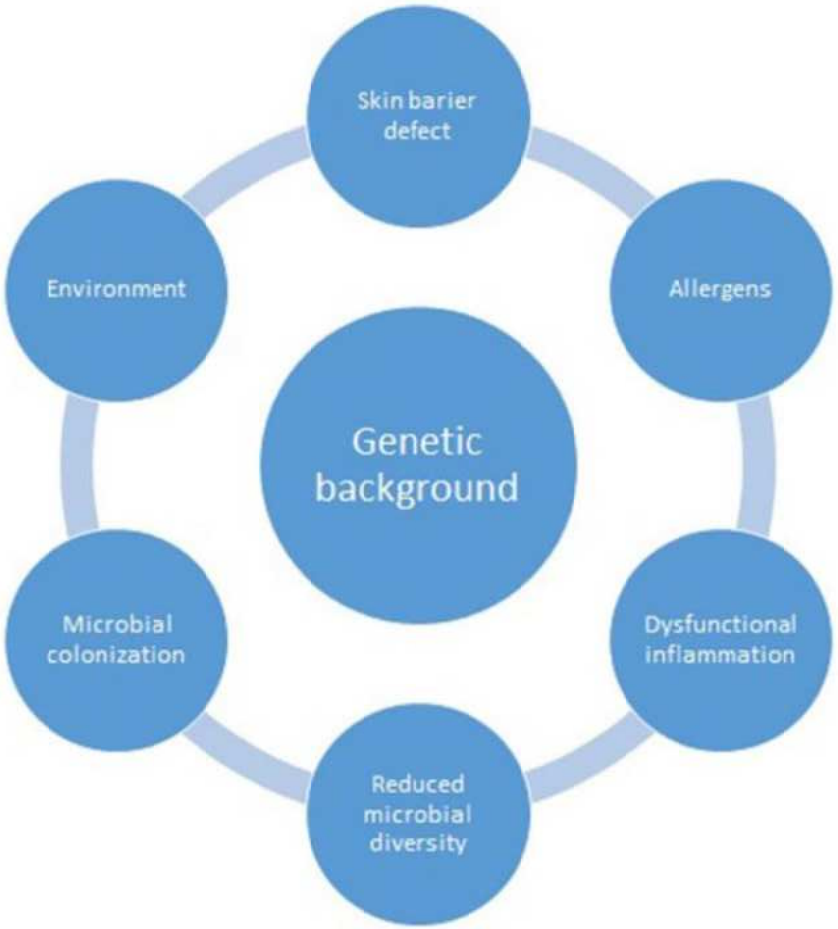
SEVERE: SCORAD >50 / or persistent eczema	Hospitalization, systemic immunosuppression: cyclosporine A [3], methotrexate [3], azathioprin [3], mycophenolate mofetil [1,3]
MODERATE: SCORAD 25-50 / or recurrent eczema	Proactive therapy with topical tacrolimus [2] or class II or III topical glucocorticosteroids [3], wet wrap therapy, UV therapy (UVB 311 nm) [1], psychosomatic counseling, climate therapy
MILD: SCORAD <25 / or transient eczema	Reactive therapy with topical glucocorticosteroids class II [2] or depending on local cofactors: topical calcineurin inhibitors [2], antiseptics incl. silver, silver coated textiles
BASELINE: Basic therapy	Educational programmes, emollients, bath oils, avoidance of clinically relevant allergens (encasings, if diagnosed by allergy tests)

Atopic dermatitis: the new psoriasis?

- AD is a systemic disorder (both cutaneous and systemic immune activation)
  - Comorbidities:
    - Allergic disorders
      - Food allergy
      - Asthma
      - Allergic rhinoconjunctivitis
      - Eosinophilic esophagitis
    - Skin infection (Staphylococcus aureus, eczema herpeticum/coxsackium, …) + extracutaneous infection (respiratory/GI/urinary)
    - Neuropsychiatric disorders (anxiety, depression, ADHD,…)
    - Obesity
    - Auto-immune disease
    - Cardiovascular disease?
    - Malignancy (lymphoma)?

Etiopathogenesis of AD

- Multifactorial
  - Genetic factors
  - Environmental factors



Arch Immunol Ther Exp 2018,66: 171-81

The molecular basis for AD

- Barrier dysfunction (“outside-in”)
- Immune abnormalities (“inside-out”)
  - Th2 mediated
  - Th22 mediated
  - (Th17 mediated)
- Role of the microbiome
- Underlying basis for itch

New targeted therapies :

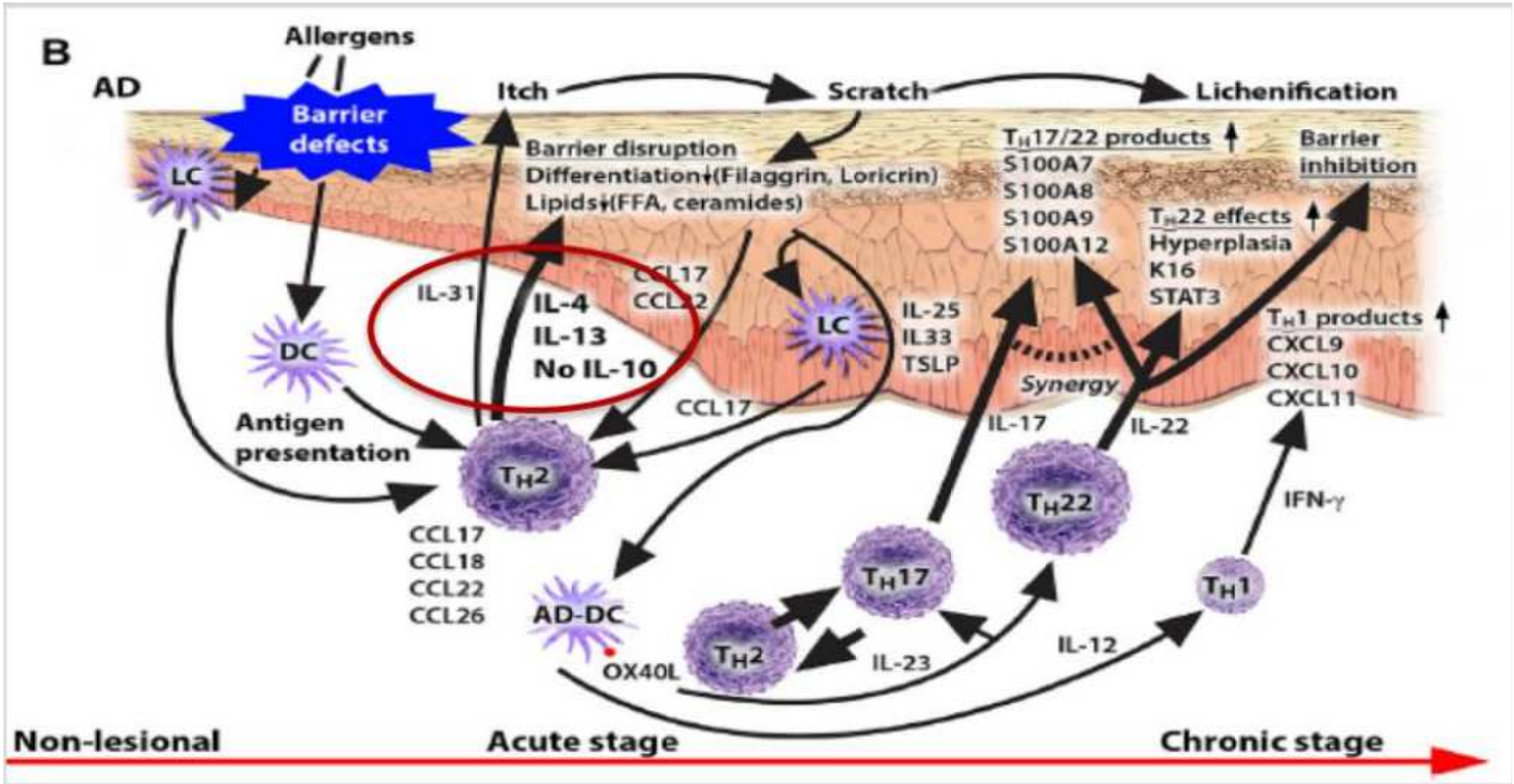
improving epidermal barrier

suppressing activated immune pathways

normalisation of microbioma

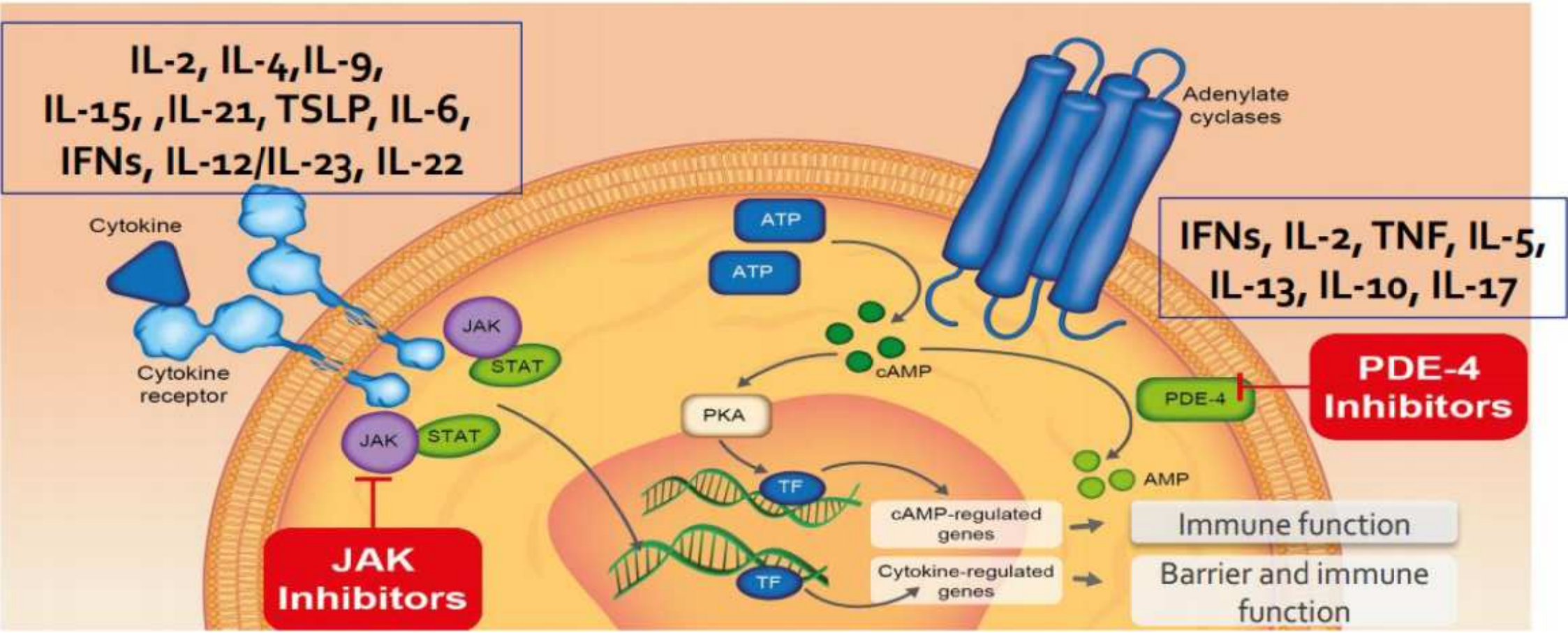
reducing itch

AD pathogenesis (biologics)



Ref :Noda et al, J Allergy Clin Immunol, 2015 Feb;135(2):324-36

AD pathogenesis (small molecules)



Adapted from Guttman E

Biologics for AD (adapted from Paller et al, J Allergy Clin Immunol 2017; 140: 633-43)

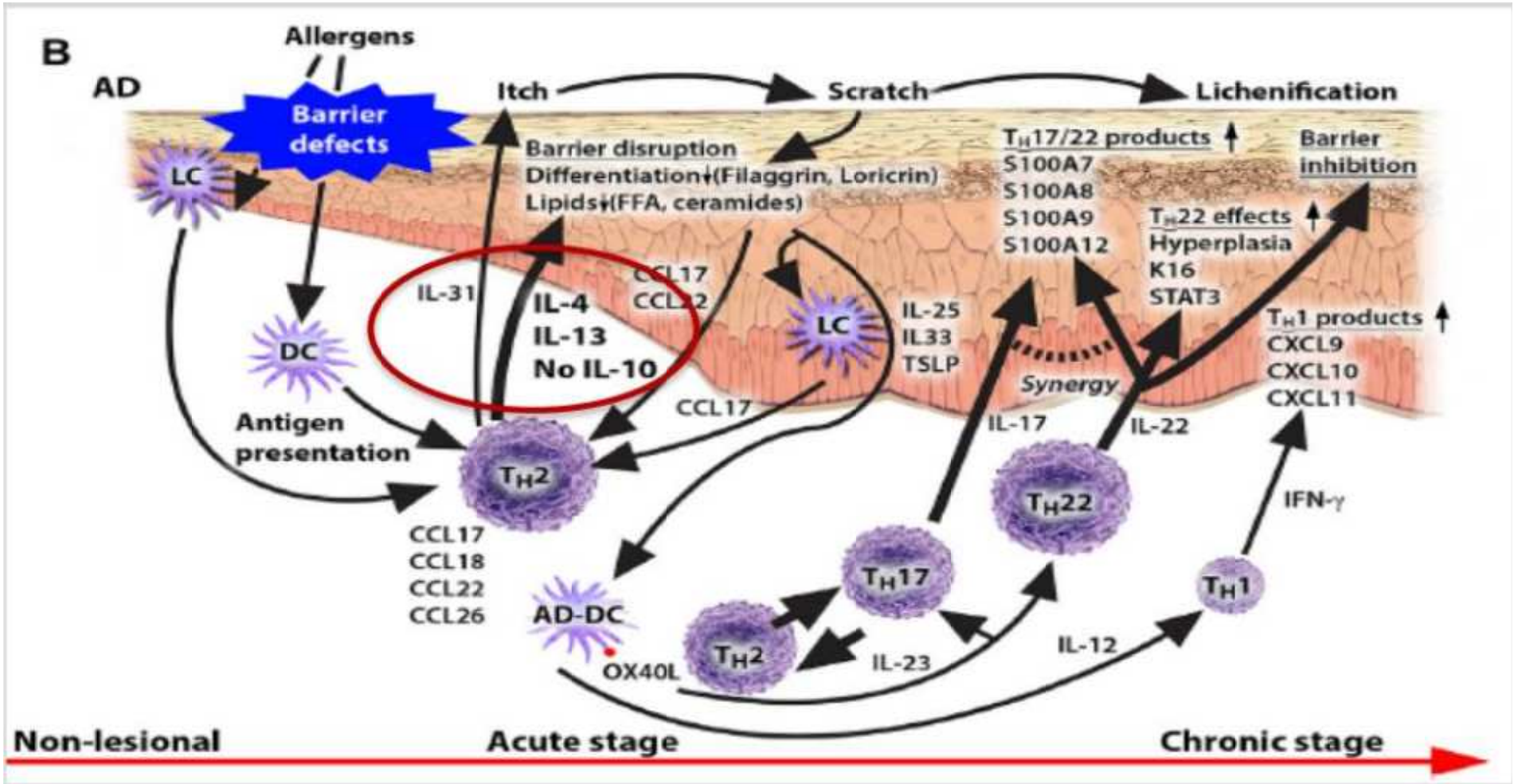
Target	Compound	Indication AD	Study Phase
IL4/IL13 (IL4Rα)	Dupilumab	Moderate-severe	Licensed for adults/ III for children
IL 13	Tralokinumab	Moderate-severe	II→III
IL 13	Lebrikizumab	Moderate-severe	II
IL 4	Pitrakinra	Moderate-severe	II→?
IL 5	Mepolizumab	Moderate-severe	II
IL17A	Secukinumab	Moderate-severe	II
IL12/IL23	Ustekinumab	Moderate-severe	No active clinical trials
IL 22	Fezakinumab	Moderate-severe	II
IgE	QGE031/ligelizumab	Moderate-severe	II→?
TSLP	Tezepelumab	Moderate-severe	IIa completed/No active clinical trials
Ora1	Anti-Ora1	Moderate-severe	II
IL31 receptor A	CIM 331/nemolizumab	Moderate-severe	II→
IL 31	BMS-981164	Moderate-severe	I

Small molecules for AD

(adapted from Paller et al, J Allergy Clin Immunol 2017; 140: 633-43)

Target	Compound	Indication AD	Study Phase
CRTH2	OC000459/QAW 039	Moderate-severe	II → stop
PDE 4	Apremilast	Moderate-severe	II → stop
H4R	ZPL389	Moderate-severe	II
JAK 1/2	Baricitinib	Moderate-severe	III
JAK 1	PF-04965842	Moderate-severe	II
JAK 1	Upadacitinib (ABT494)	Moderate-severe	III
NK1R	VLY-686/tradipant	Moderate-severe	II
NK1R	Serlopitant	Moderate-severe	II

AD pathogenesis (biologics)



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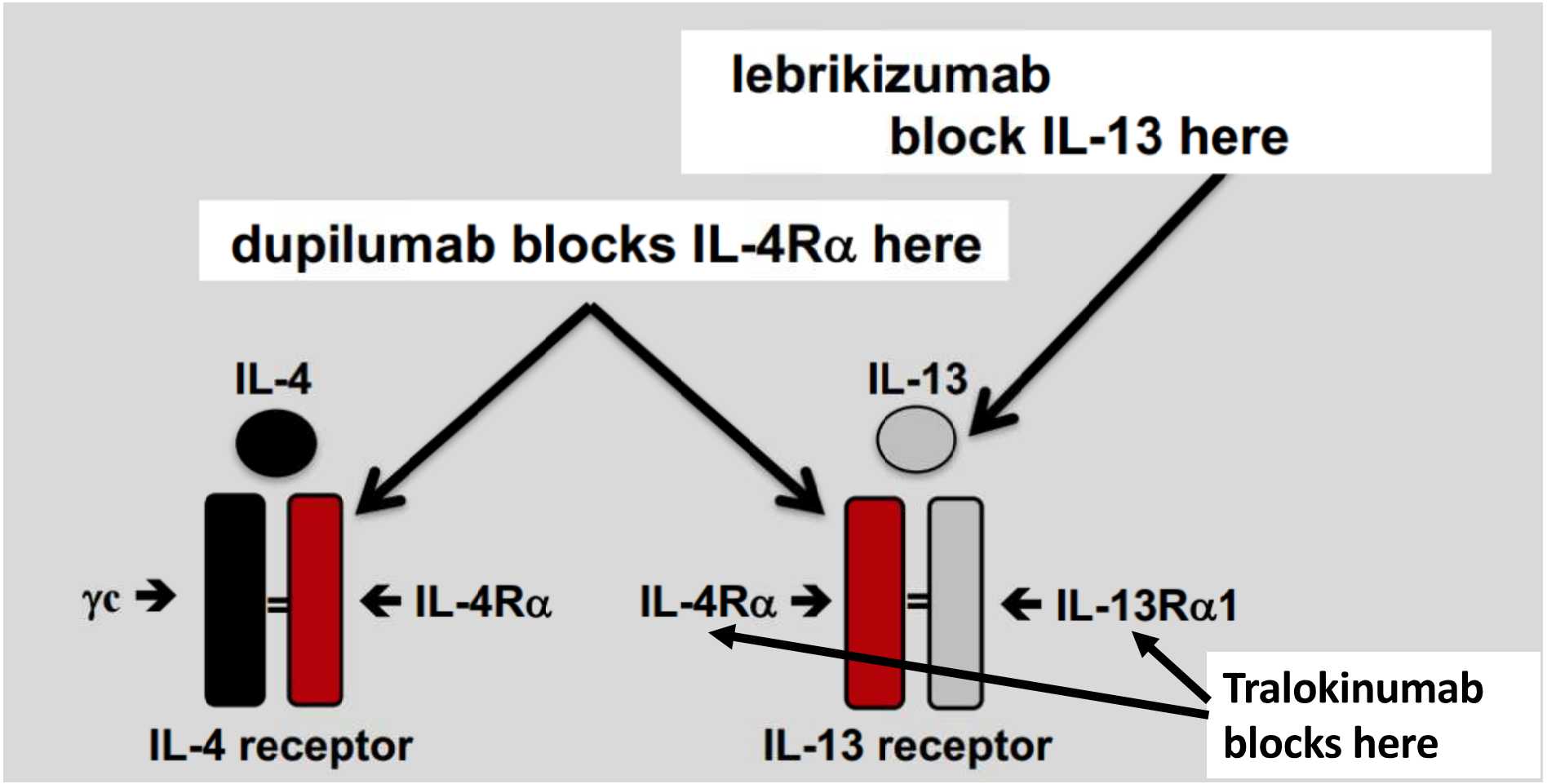
Biologicals for AD : IL 4/13



Biologicals for AD : dupilumab

- Dupilumab impacts both inflammation and barrier dysfunction in AD
- Also works in astma (phase III), chronic rhinosinusitis with nasal polyposis (phase III) and eosinophilic esophagitis (phase II)
- Dose: 300mg /2ww
- Long term data available:
  - LIBERTY AD SOLO-CONTINUE: 36 weeks
  - CHRONOS 52 weeks + TCS
  - OLE: up to 3 years (open label extension study)

Biologicals for AD : dupilumab

- Low immunogenicity
  - <10% antidrug AB
  - <1% persistent

- Treatment interruption did not impact long term tolerability of dupilumab
  - Retreated patients had higher ADA incidence
  - This analysis could not anticipate what happens in multiple retreatments (Beck LA, poster at Society for Investigative Dermatology 2017)

Biologicals for AD : dupilumab

- Adverse events:

– **Conjunctivitis (5-10%)**
  - not in astma or nasal polyposis
  - = inflammation of the anterior conjunctiva and hyperemia of the limbus
  - R/fluorometholone 0.1% eye drops or off-label with tacrolimus 0.03% eye ointment

– Injection site reactions

– Headaches

– Previous studies: increase in HSV infections of the skin
  - ↔ decrease in skin infections and eczema herpeticum (J Am Acad Dermatol 2018: 78:62-9)

– No medication-related serious adverse events

- Studies in children (6-18yr phase 3) underway

Biologicals for AD: tralokinumab

J Allergy Clin Immunol. 2018 Jun 12. pii: S0091-6749(18)30850-9. doi: 10.1016/j.jaci.2018.05.029. [Epub ahead of print]

Treatment of atopic dermatitis with tralokinumab, an anti-IL-13 mAb.

Wollenberg A[1], Howell MD[2], Guttman-Yassky E[3], Silverberg JI[4], Kell C[5], Ranade K[2], Moate R[6], van der Merwe R[7].

- Human monoclonal antibody to block IL-13
- Phase 2b (+TCS)
- Adults age 18-75 years
- Primary endpoint: % change in EASI, % achieving IGA 0 or 1+2point improvement at week 12
- Conclusion: Participants treated with 300 mg of tralokinumab every 2ww demonstrated improvements in SCORAD, Dermatology Life Quality Index, and pruritus numeric rating scale (7-day mean) scores versus placebo.

Biologicals for AD: tralokinumab

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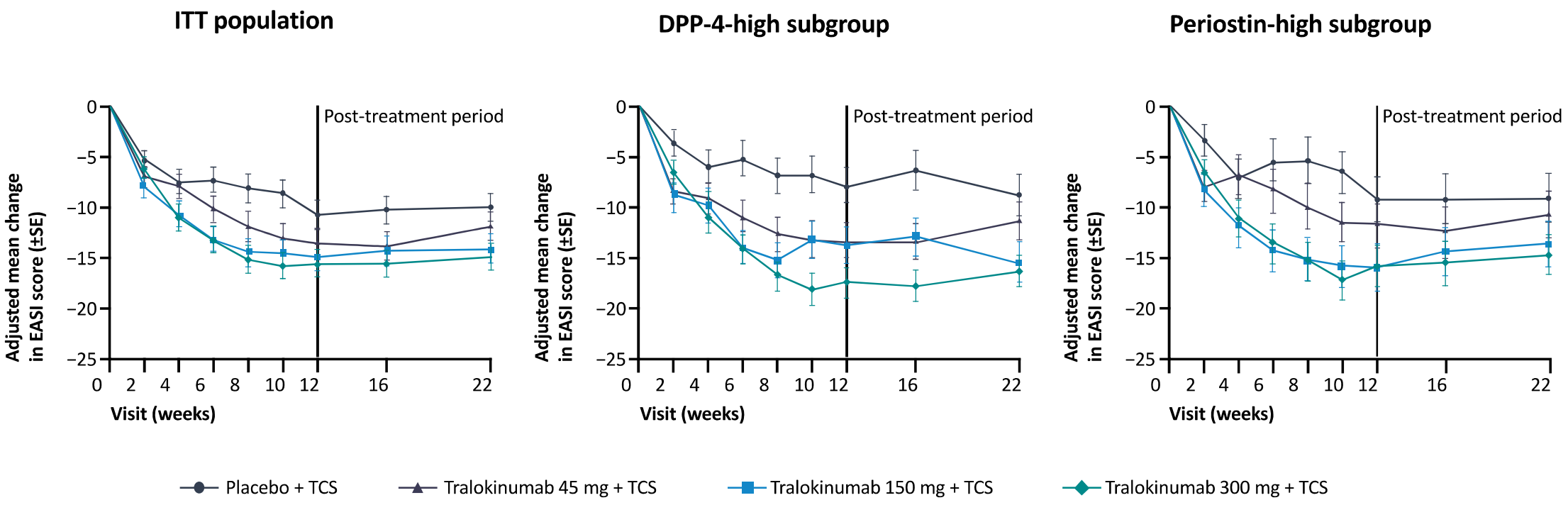
- Side effects
  - No conjunctivitis or other eye disorders
  - Upper respiratory tract infection (3,9%) and headache (2%) most frequent

- No significant formation of ADA

Greater Benefit (EASI) Seen in Subgroups with High IL-13 Activity



Greater treatment responses experienced by participants with increased IL-13 activity (high DPP-4 / periostin) support a key role in AD pathophysiology

J Allergy Clin Immunol 2018 Jun 12 (epub ahead of print)

Biologicals for AD: lebrikizumab

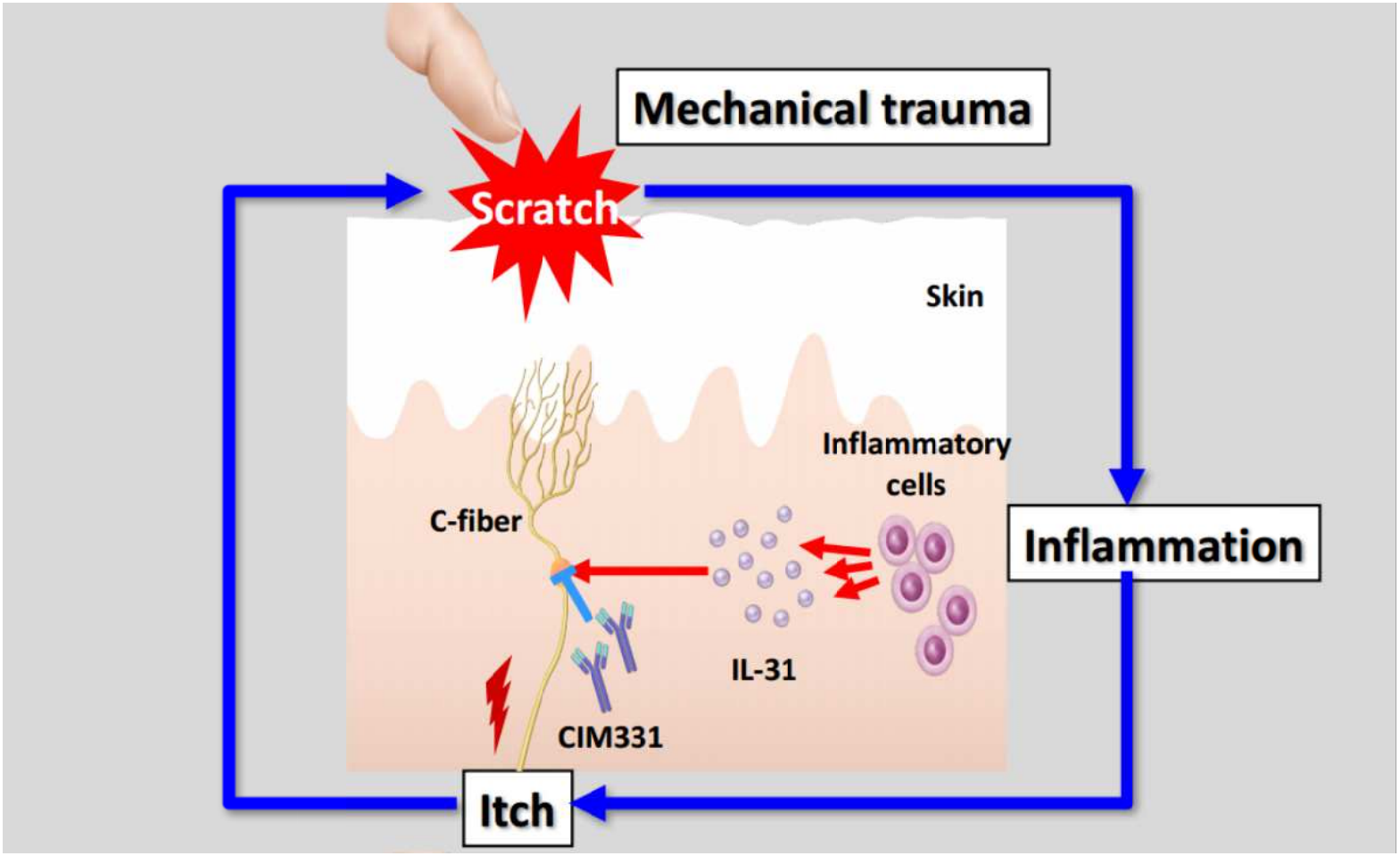
J Am Acad Dermatol. 2018 May;78(5):863-871.e11. doi: 10.1016/j.jaad.2018.01.017. Epub 2018 Jan 17.

Efficacy and safety of lebrikizumab (an anti-IL-13 monoclonal antibody) in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical corticosteroids: A randomized, placebo-controlled phase II trial (TREBLE).

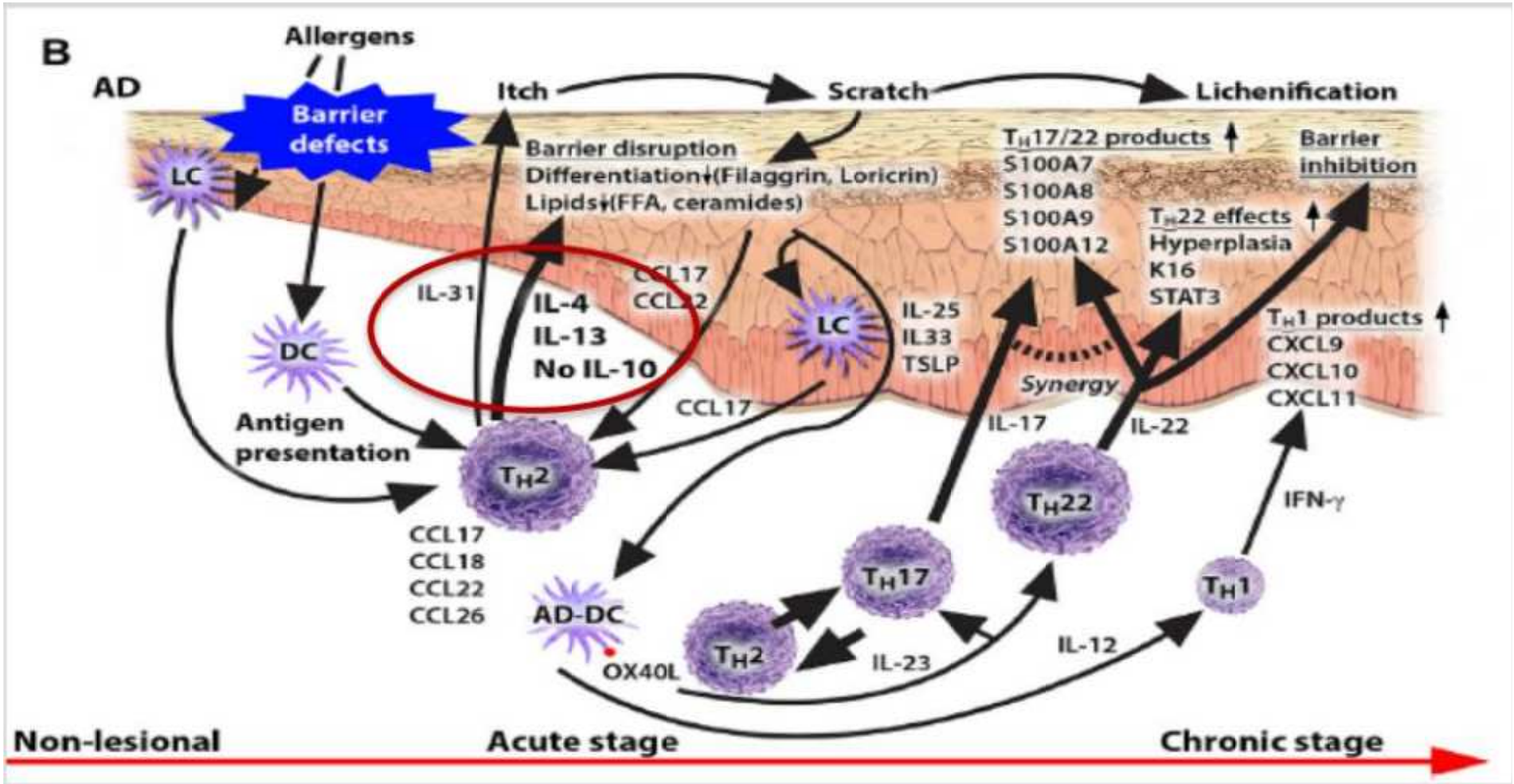
Simpson EL[1], Flohr C[2], Eichenfield LF[3], Bieber T[4], Sofen H[5], Taïeb A[6], Owen R[7], Putnam W[7], Castro M[7], DeBusk K[7], Lin CY[7], Voulgari A[8], Yen K[9], Omachi TA[10].

- Anti-IL-13 monoclonal antibody
- TREBLE: phase 2 study (+ TCS)
- Adults age 18-75
- Primary endpoint: achieving EASI 50 at week 12
- At week 12, significantly more patients achieved EASI-50 with lebrikizumab 125 mg every 4 weeks (82.4%) than placebo every 4 weeks (62.3%)

Biologicals for AD: IL 31: nemolizumab



AD pathogenesis (biologics)



Ref :Noda et al, J Allergy Clin Immunol, 2015 Feb;135(2):324-36

Biologicals for AD: IL 31: nemolizumab

J Allergy Clin Immunol. 2018 May 10. pii: S0091-6749(18)30698-5. doi: 10.1016/j.jaci.2018.03.018. [Epub ahead of print]

Nemolizumab in patients with moderate-to-severe atopic dermatitis: Randomized, phase II, long-term extension study.

Kabashima K[1], Furue M[2], Hanifin JM[3], Pulka G[4], Wollenberg A[5], Galus R[6], Etoh T[7], Mihara R[8], Nakano M[8], Ruzicka T[5].

- Anti-IL31 receptor A antibody

- Phase 2:
  - Reduction in pruritus up to 60%
  - Improvement quantity and quality of sleep
  - Improved QoL
  - Improvement in dermatitis

Biologicals for AD: nemolizumab

TABLE II. Patients with a 25%, 50%, and 75% improvement from baseline in pruritus VAS and EASI scores at week 12 and week 64 (ITT population who received nemolizumab in part A, includes data after rescue therapy)

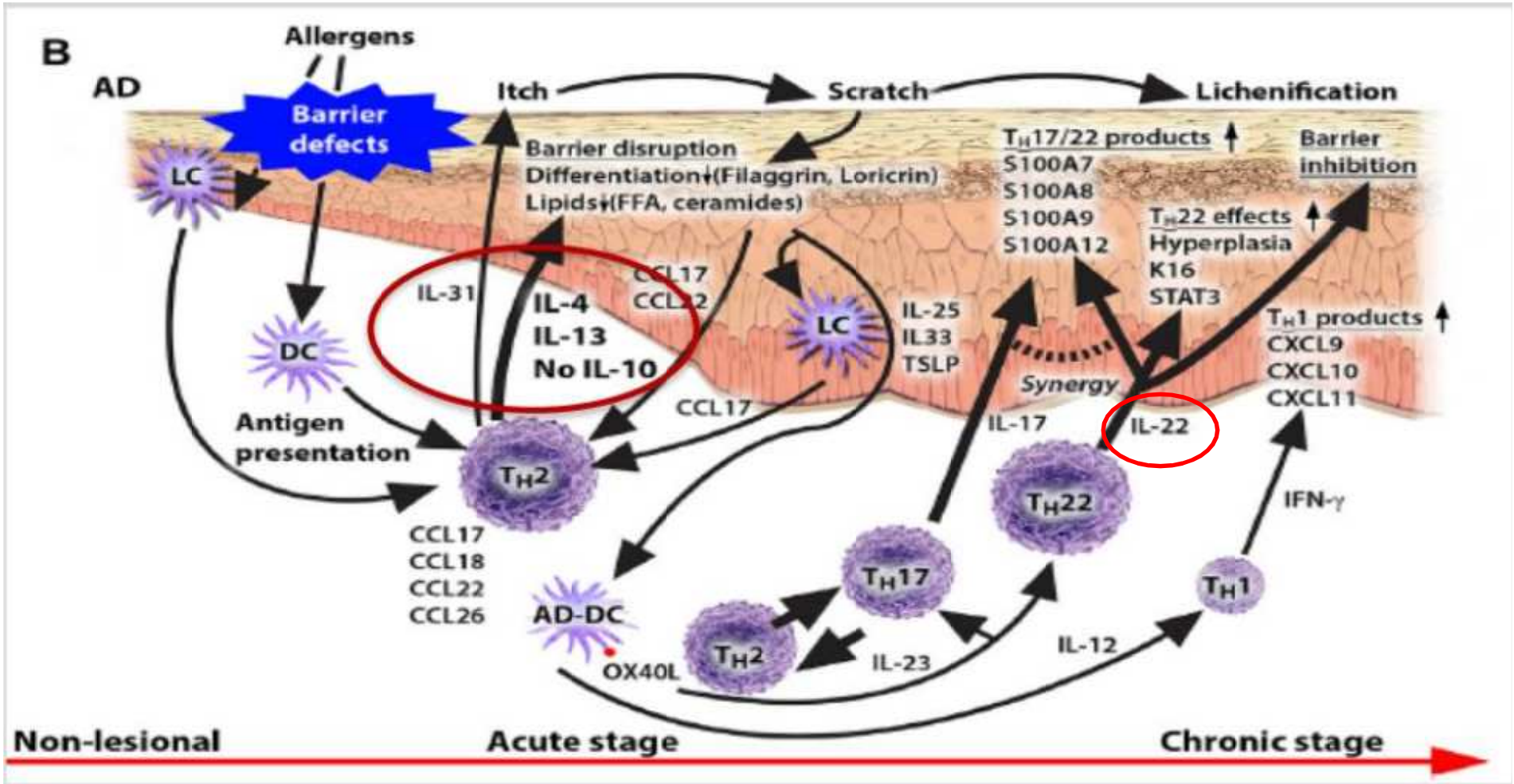
	Nemolizumab							
	0.1 mg/kg Q4W (n = 53)		0.5 mg/kg Q4W (n = 54)		2.0 mg/kg Q4W (n = 52)		2.0 mg/kg Q8W (n = 52)	
End point	Week 12	Week 64	Week 12	Week 64	Week 12	Week 64	Week 12	Week 64
Pruritus VAS	(n = 45)	(n = 29)	(n = 45)	(n = 26)	(n = 46)	(n = 28)	(n = 39)	(n = 18)
25%	35 (78)	26 (90)	38 (84)	26 (100)	42 (91)	26 (93)	33 (85)	17 (94)
50%	22 (49)	23 (79)	32 (71)	26 (100)	31 (67)	22 (79)	29 (74)	16 (89)
75%	8 (18)	19 (66)	24 (53)	24 (92)	21 (46)	19 (68)	18 (46)	14 (78)
EASI	(n = 45)	(n = 31)	(n = 46)	(n = 28)	(n = 46)	(n = 29)	(n = 37)	(n = 19)
25%	27 (60)	27 (87)	32 (70)	28 (100)	34 (74)	27 (93)	27 (73)	17 (89)
50%	21 (47)	23 (74)	25 (54)	20 (71)	22 (48)	26 (90)	16 (43)	15 (79)
75%	13 (29)	21 (68)	18 (39)	19 (68)	11 (24)	19 (66)	8 (22)	14 (74)

Data are shown as numbers (percentages).
ITT, Intent-to-treat.

J Allergy Clin Immunol 2018 May 10 (epub ahead of print)

Treatment related AE: exacerbation of AD (8%), upper respiratory tract infection (4%), nasopharyngitis (4%), peripheral edema (3%), increased CK (3%), injection site reaction (2%)

AD pathogenesis (biologics)



Ref :Noda et al, J Allergy Clin Immunol, 2015 Feb;135(2):324-36

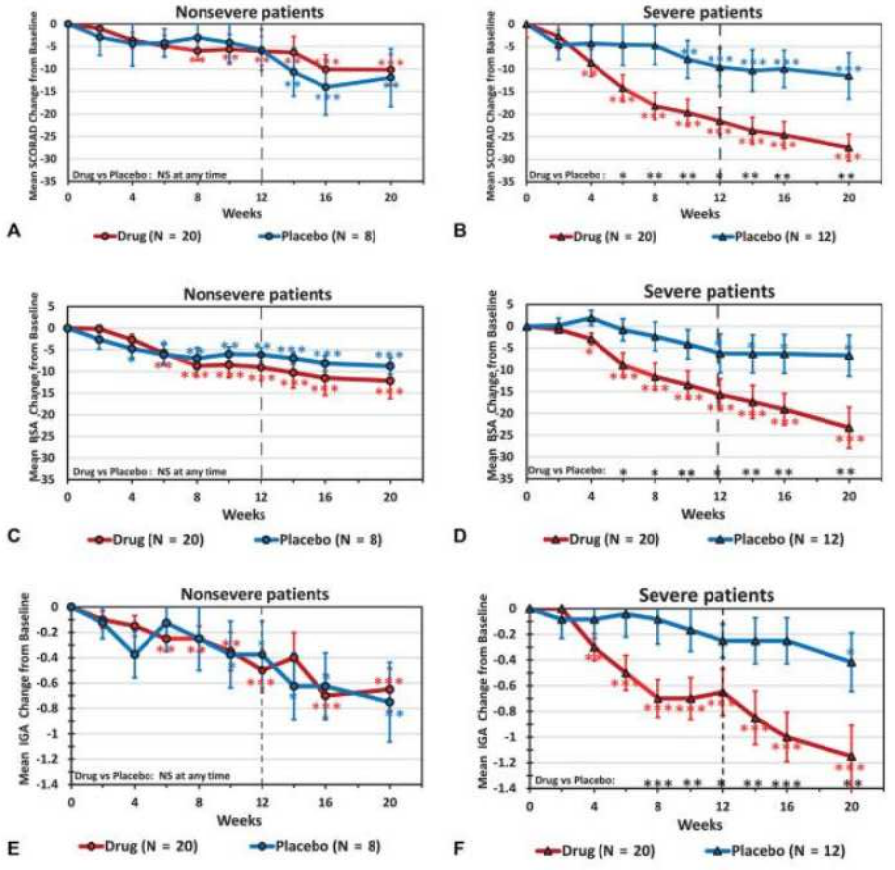
Biologicals for AD: IL 22: Fezakinumab

J Am Acad Dermatol. 2018 May;78(5):872-881.e6. doi: 10.1016/j.jaad.2018.01.016. Epub 2018 Jan 17.

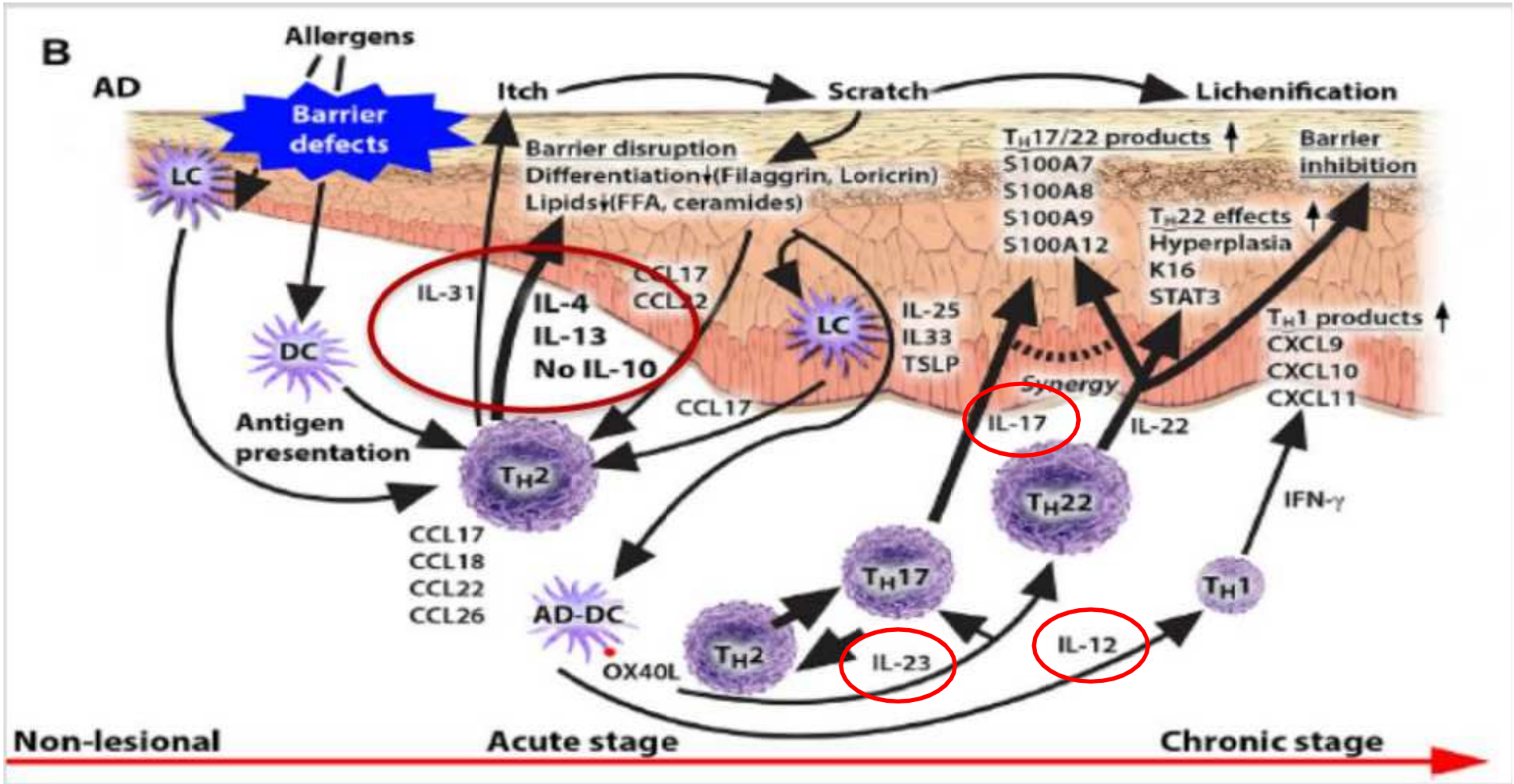
Efficacy and safety of fezakinumab (an IL-22 monoclonal antibody) in adults with moderate-to-severe atopic dermatitis inadequately controlled by conventional treatments: A randomized, double-blind, phase 2a trial.

Guttman-Yassky E[1], Brunner PM[2], Neumann AU[3], Khattri S[4], Pavel AB[4], Malik K[4], Singer GK[4], Baum D[4], Gilleaudeau P[2], Sullivan-Whalen M[2], Rose S[4], Jim On S[4], Li X[2], Fuentes-Duculan J[2], Estrada Y[4], Garcet S[2], Traidl-Hoffmann C[5], Krueger JG[2], Lebwohl MG[4].

- AE: upper respiratory tract infections



AD pathogenesis (biologics)



Ref :Noda et al, J Allergy Clin Immunol, 2015 Feb;135(2):324-36

Biologicals for AD: IL 17/23

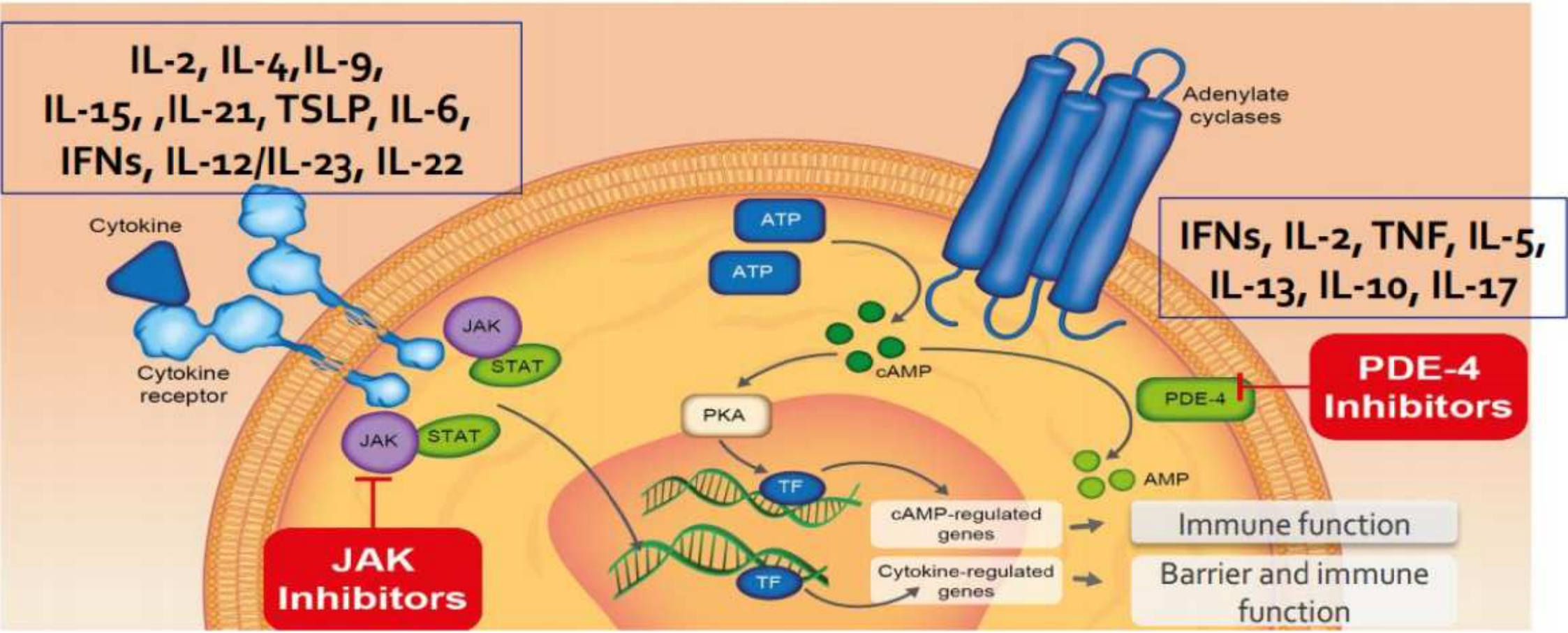
- Ustekinumab (IL12/23): no effect
  - Khattri S et al, Exp Dermatol 2017;26:28-35
  - Saeki H et al, Br J Dermatol 2017;177:419-27 (Japanese pts with increased Th17!)

- Secukinumab (IL17A): current trial NCT 02594098

Others still further down the road…

- MOR-106 is a first class mAB against IL 17C: phase 1 dose finding study
- Proof of concept phase 2a trial of ANB020 (anti-IL33) in AD

Small molecules for AD: JAK inhibitor



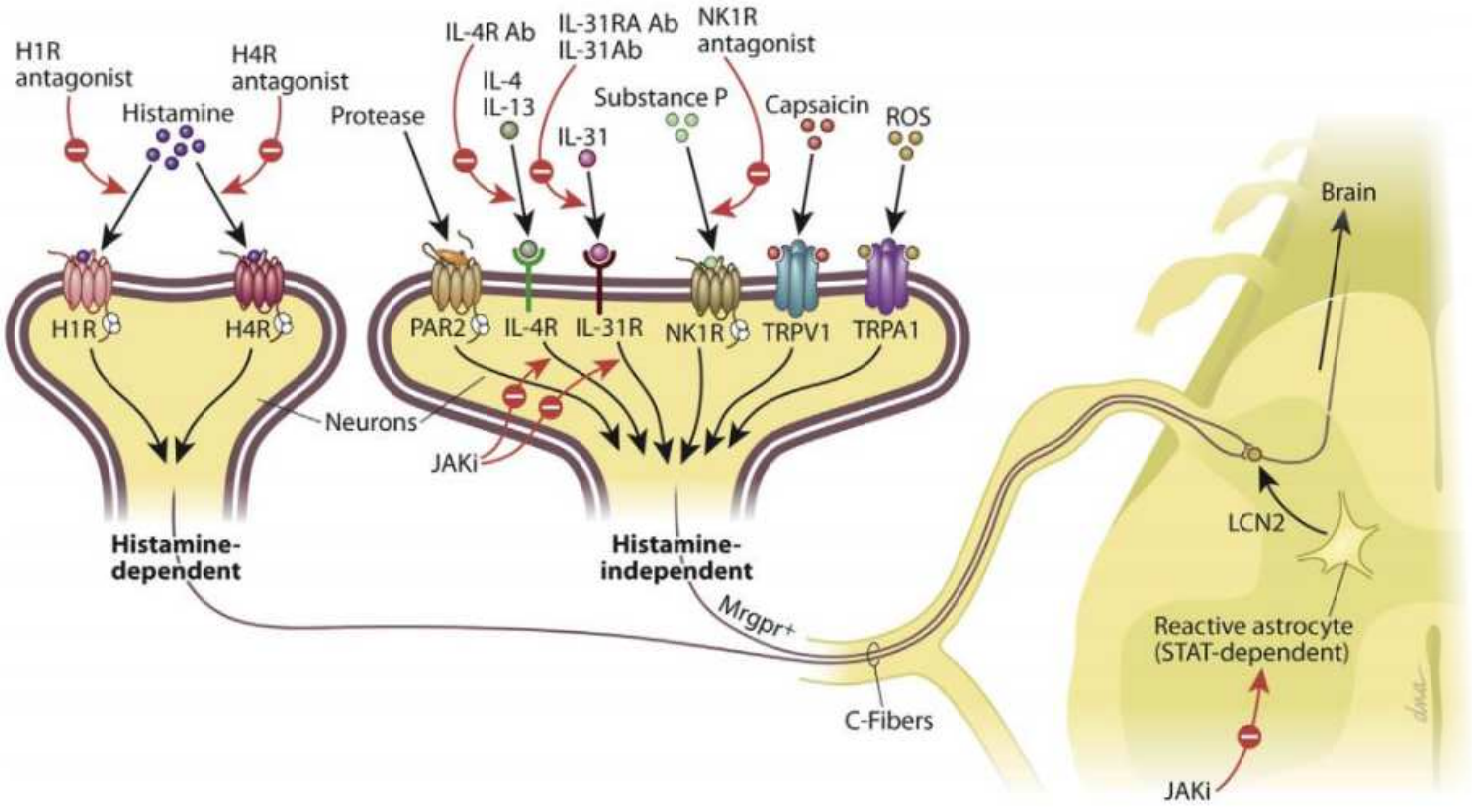
Adapted from Guttman E

Small molecules for AD: JAK inhibitor

- Baricitinib (JAK1/2)
  - Phase 2 (J Am Acad Dermatol 2018 Feb 1 (epub ahead of print))
  - +TCS
  - EASI 50 at 16 weeks: Baricitinib 4mg/d 61%-placebo 37%
- Upadacitinib (JAK 1)
  - Phase 2b (E Guttmann, poster AAD 2018)
    - mean EASI improvement of 74,4% with 30mg upadacitinib/d compared to 23% with placebo
    - No serious adverse events
      - Upper respiratory tract infections >10%
    - Rapid onset of action (significant improvement after 2w, max efficacy after 4w)
- CAVE: oral tofacitinib: adverse events due to long term immunosuppression limit its use in AD

Small molecules for AD: NK1R

- Tradipant (phase 2 in trial NCT 02651714)
- Serlopitant (phase 2 in trial NCT 02975206)
  - Neurokinin 1 receptor antagonist
  - Inhibits substance P



From : Paller et al, J Allergy Clin Immunol 2017; 140: 633-43

Small molecules for AD: H4R

- ZPL-3893787
  - Antagonizing histamine H4 receptor
  - Histamine
    - Inhibits terminal differentiation of keratinocytes
    - Impairs skin barrier in AD
    - Pruritus induction
    - But classical anti-H1 and anti-H2 disappointing in itch in AD

  - H4R antagonist: RCT 98 pt moderate/severe AD (Werfel T et al, J Allergy Clin Immunol 2018, epub ahead of print)
    - 50% reduction in EASI compared to 27% placebo
    - Well tolerated, no reduction of circulating granulocytes

Conclusion

- The landscape of systemic treatment of AD is rapidly changing from broad immunosuppression to targeted treatments with biologicals or small molecules

- Currently dupilumab is the only biological marketed/approved for AD

The Future

- Which treatment for which AD patient?
  - Comparing biomarkers with individual responses to experimental agents
    - Cfr tralokinumab
  - Group AD into subphenotypes
    - Less Th17 in European-American and African-American AD compared to pediatric and Asian AD
    - No Th1 increase in pediatric AD and African-American AD
- Treatment duration? Tapering?