아토피피부염 치료의 최신지견

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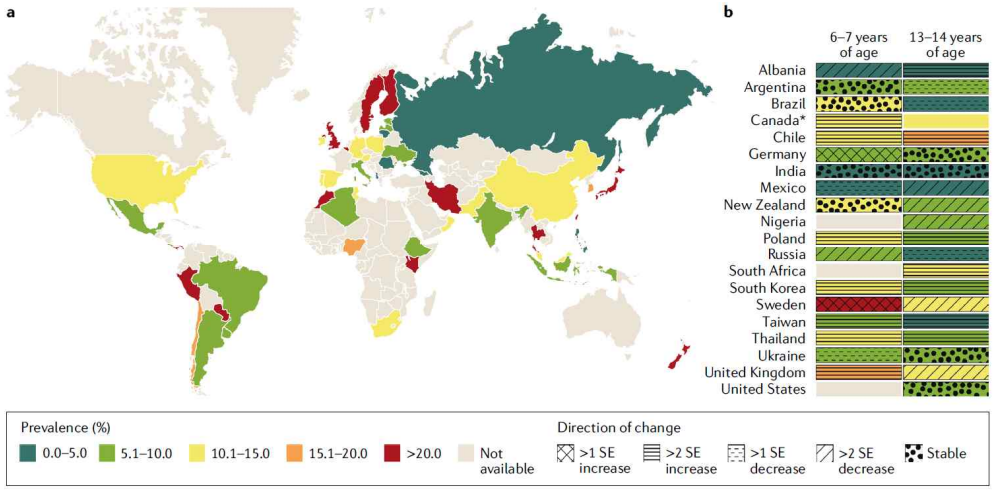
Short Story of Atopic Dermatitis (AD)

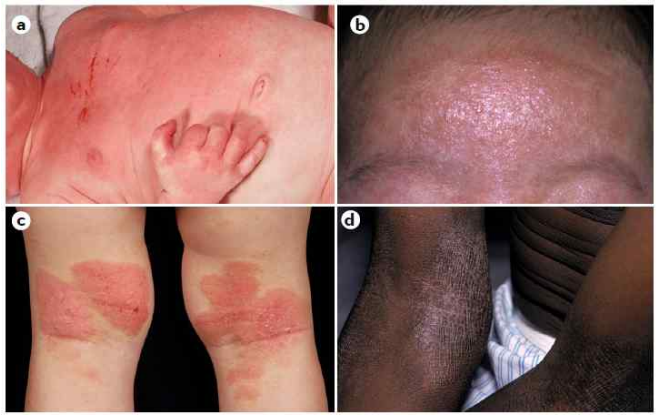
- **High prevalence**:

  Lifetime prevalence of 15-20% in developed countries[1]



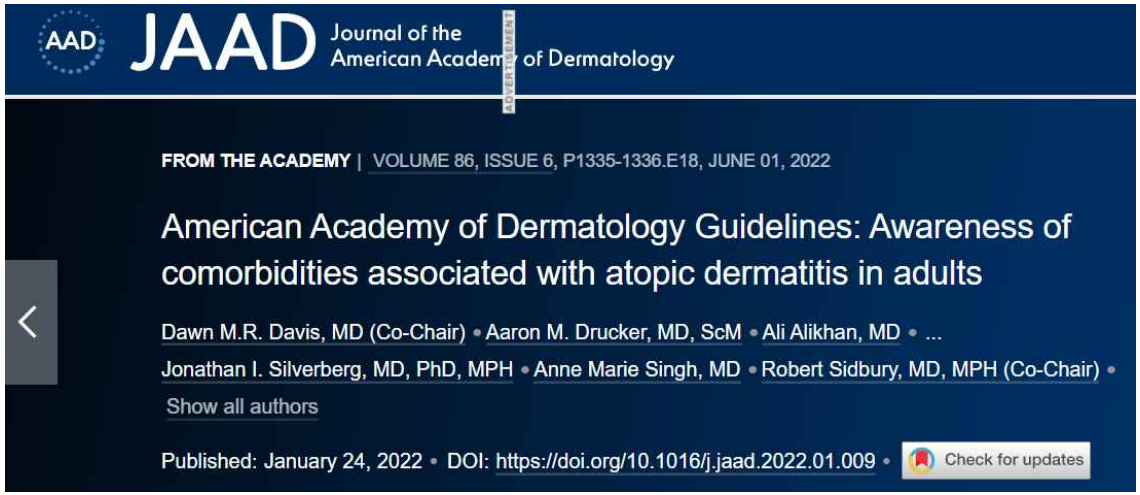
- **Variable course** and **severity**[2]

- **Significant disease burden** and **comorbidities**[2,3]



1. Deckers et al. Investigating international time trends in the incidence and prevalence of atopic eczema 1990-2010: a systematic review of epidemiological studies. PLoS ONE 7, e39803 (2012). 2. Simpson et al. Update on epidemiology, diagnosis, and disease course of AD. Semin Cutan Med Surg. 2016 Jun;35(5 Suppl):S84-8. 3. Photos from Weidinger et al. Atopic dermatitis. Nature Reviews Disease Primers volume 4, Article number: 1 (2018)

Update to AAD Guidelines on AD Comorbidities



Objective: To appraise evidence of the association between AD and comorbidities among adults

Methods:

- Multidisciplinary work group conducted a systematic review of the association between AD and selected comorbidities.
- Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) was used to assess the certainty of evidence.
- The Work Group drafted statements of association based on the overall quality of evidence.

Davis et al. J Am Acad Dermatol 2022;86:1336.e1-18.

Update to AAD Guidelines on AD Comorbidities

Clinical question: **"Among adults, what is the association between AD and…"**

- Atopic and allergic conditions
  - Asthma
  - Food allergy
  - Allergic rhinitis
  - Allergic conjunctivitis
  - Eosinophilic esophagitis
- Immune-mediated conditions
  - AA
  - Urticaria
- Mental health and substance use
  - Depression
  - Anxiety
  - Suicide
  - Alcohol use disorders
  - Cigarette smoking
  - ADHD
  - Autism spectrum disorders
- Cardiovascular disease
  - Coronary artery disease
  - Congestive heart failure
  - Peripheral artery disease
  - Thromboembolic disease
  - Myocardial infarction
  - Stroke
  - Cardiovascular death
  - Hypertension
- Metabolic disorders
  - Diabetes
  - Dyslipidemia
  - Obesity
  - Metabolic syndrome
- Bone health
  - Osteoporosis
  - Bone fractures
- Skin infection

Davis et al. J Am Acad Dermatol 2022;86:1336.e1-18.

Update to AAD Guidelines on AD Comorbidities

Table II. Strength of statements and supporting evidence: Wording and implications

Statement wording	Overall certainty of supporting evidence	Implication
Is associated	High or moderate	Clear evidence of an important large effect
Is not associated	High or moderate	Clear evidence of no association
Probably associated	High or moderate	Evidence of a moderate effect
Probably not associated	High or moderate	Evidence of small or unimportant effect
May be associated	Low	Evidence of a large, moderate, or small effect based on low quality evidence
May not be associated	Low	Evidence of no association based on low certainty evidence
Uncertain association	Any quality	Evidence of any magnitude of effect from very low certainty evidence or imprecise or inconsistent effect estimates from evidence of any certainty

Strength of evidence	Wording	Implication [1,2,4]
High	"High certainty evidence"	Very confident that the true magnitude of association lies close to that of the estimate
Moderate	"Moderate certainty evidence"	Moderately confident in the estimate of association, but there is a possibility that it is substantially different
Low	"Low certainty evidence"	Confidence in the estimate is limited; the true magnitude of association may be substantially different from the estimate
Very low	"Very low certainty evidence"	The estimate is very uncertain; the true magnitude of association may be substantially different from the estimate

Davis et al. J Am Acad Dermatol 2022;86:1336.e1-18.

Update to AAD Guidelines on AD Comorbidities

Atopic and allergic conditions	Association	Strength of evidence
Asthma	Is associated	Moderate
Food allergies	Is associated	High
Allergic rhinitis	Is associated	Moderate
Allergic conjunctivitis	Uncertain	Low
Eosinophilic esophagitis	May be associated	Low

Immune-mediated conditions	Association	Strength of evidence
Alopecia areata	Is associated	Moderate
Urticaria	Is associated	Moderate

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Davis et al. J Am Acad Dermatol 2022;86:1336.e1-18.

Disorder	Atopic dermatitis (UK Working Party criteria)							
	Frequency (weighted prevalence[a])		Crude RR (95% CI)	*P* value	Model 1[b]		Model 2[b]	
	No	Yes			Adjusted RR (95% CI)[a]	*P* value	Adjusted RR (95% CI)[a]	*P* value
Asthma								
No	1,034 (71.2%)	314 (50.2%)	1.00 (ref)	—	1.00 (ref)	—		
Yes	437 (28.8%)	288 (49.8%)	1.73 (1.53–1.93)	<.0001	1.68 (1.48–1.88)	<.0001		
Hay fever								
No	501 (37.2%)	70 (13.0%)	1.00 (ref)	—	1.00 (ref)	—		
Yes	970 (62.8%)	532 (87.0%)	1.39 (1.32–1.46)	<.0001	1.47 (1.37–1.57)	<.0001		
Food allergy								
No	1,964 (93.9%)	518 (85.4%)	1.00 (ref)	—	1.00 (ref)	—		
Yes	143 (6.1%)	83 (14.6%)	2.39 (1.79–2.99)	<.0001	2.45 (1.79–3.06)	<.0001		

PO-SCORAD	Comorbid condition							
	Frequency (weighted prevalence[a])		Crude RR (95% CI)	*P* value	Model 1[b]		Model 2[b]	
	No	Yes			Adjusted RR (95% CI)	*P* value	Adjusted RR (95% CI)	*P* value
Asthma								
No AD	1,034 (71.2%)	437 (28.8%)	1.00 (ref)	—	1.00 (ref)	—		
Mild	195 (62.4%)	124 (37.6%)	1.31 (1.09–1.52)	.002	1.34 (1.12–1.56)	.0008		
Moderate	105 (41.4%)	132 (58.6%)	2.04 (1.77–2.30)	<.0001	1.94 (1.66–2.21)	<.0001		
Severe	14 (26.2%)	32 (73.8%)	2.56 (2.12–3.01)	<.0001	2.38 (1.91–2.85)	<.0001		
Hay fever								
No AD	501 (37.2%)	970 (62.8%)	1.00 (ref)	—	1.00 (ref)	—		
Mild	30 (9.8%)	289 (90.2%)	1.44 (1.36–1.51)	<.0001	1.51 (1.40–1.62)	<.0001		
Moderate	34 (15.8%)	203 (84.2%)	1.34 (1.25–1.43)	<.0001	1.44 (1.32–1.55)	<.0001		
Severe	6 (16.5%)	40 (83.5%)	1.33 (1.17–1.49)	.002	1.44 (1.26–1.61)	.0002		
Food allergy								
No AD	1,964 (93.9%)	143 (6.1%)	1.00 (ref)	—	1.00 (ref)	—		
Mild	288 (90.5%)	31 (9.5%)	1.55 (0.95–2.14)	.06	1.48 (0.89–2.07)	.08		
Moderate	200 (85.7%)	36 (14.3%)	2.34 (1.54–3.13)	<.0001	2.40 (1.54–3.27)	<.0001		
Severe	30 (57.1%)	16 (42.9%)	7.01 (4.64–9.37)	<.0001	8.49 (5.44–11.54)	<.0001		

Update to AAD Guidelines on AD Comorbidities

Mental health and substance use	Association	Strength of evidence
Clinician-diagnosed depression	Is associated	Moderate
Clinician-diagnosed anxiety	Is associated	Moderate
Suicide	May be associated	Low
Alcohol abuse disorders	May be associated	Low
Cigarette smoking	May be associated	Low
ADHD	May be associated	Low
Autism spectrum disorder	Uncertain	Very low

Davis et al. J Am Acad Dermatol 2022;86:1336.e1-18.

아토피피부염의 치료 – Korean guideline

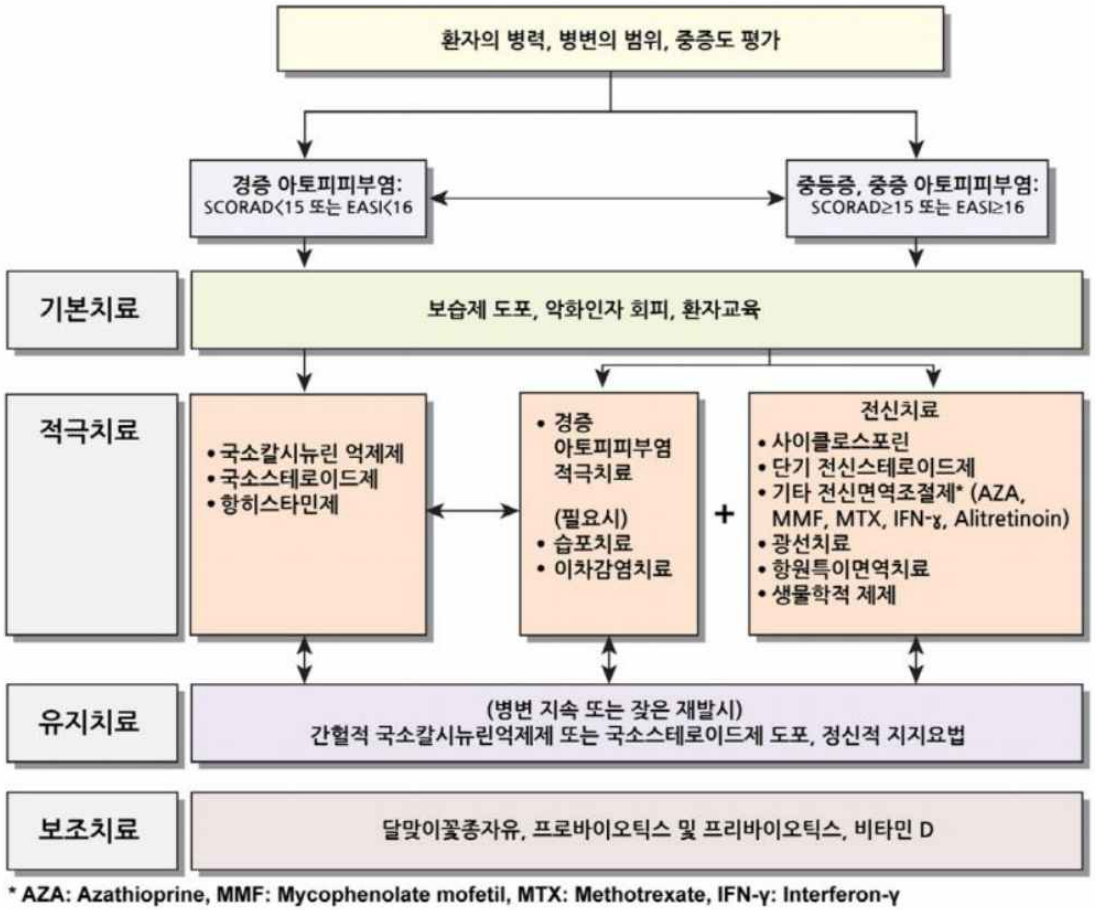
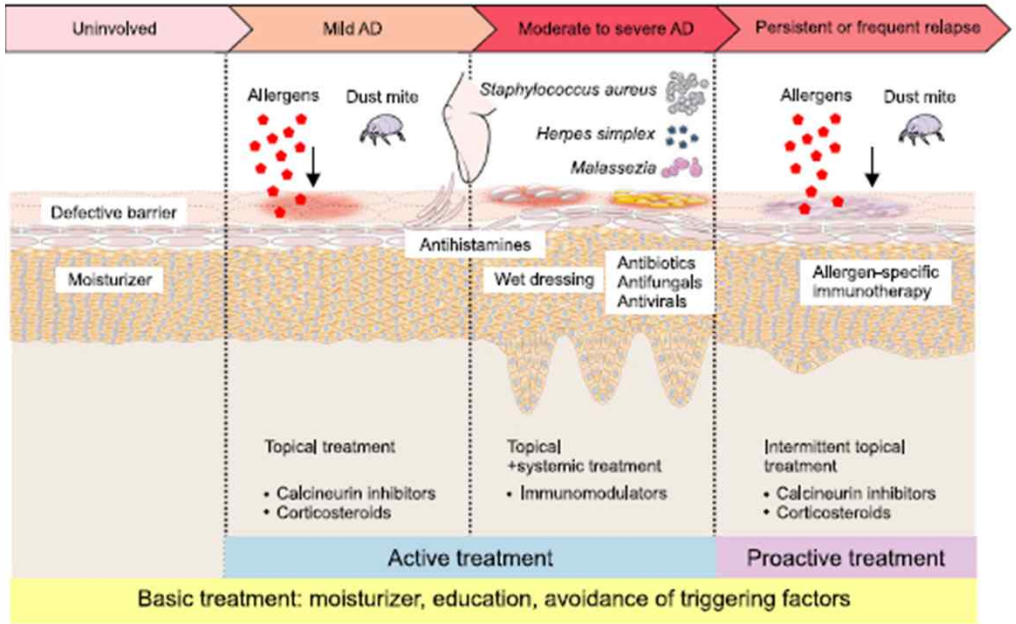


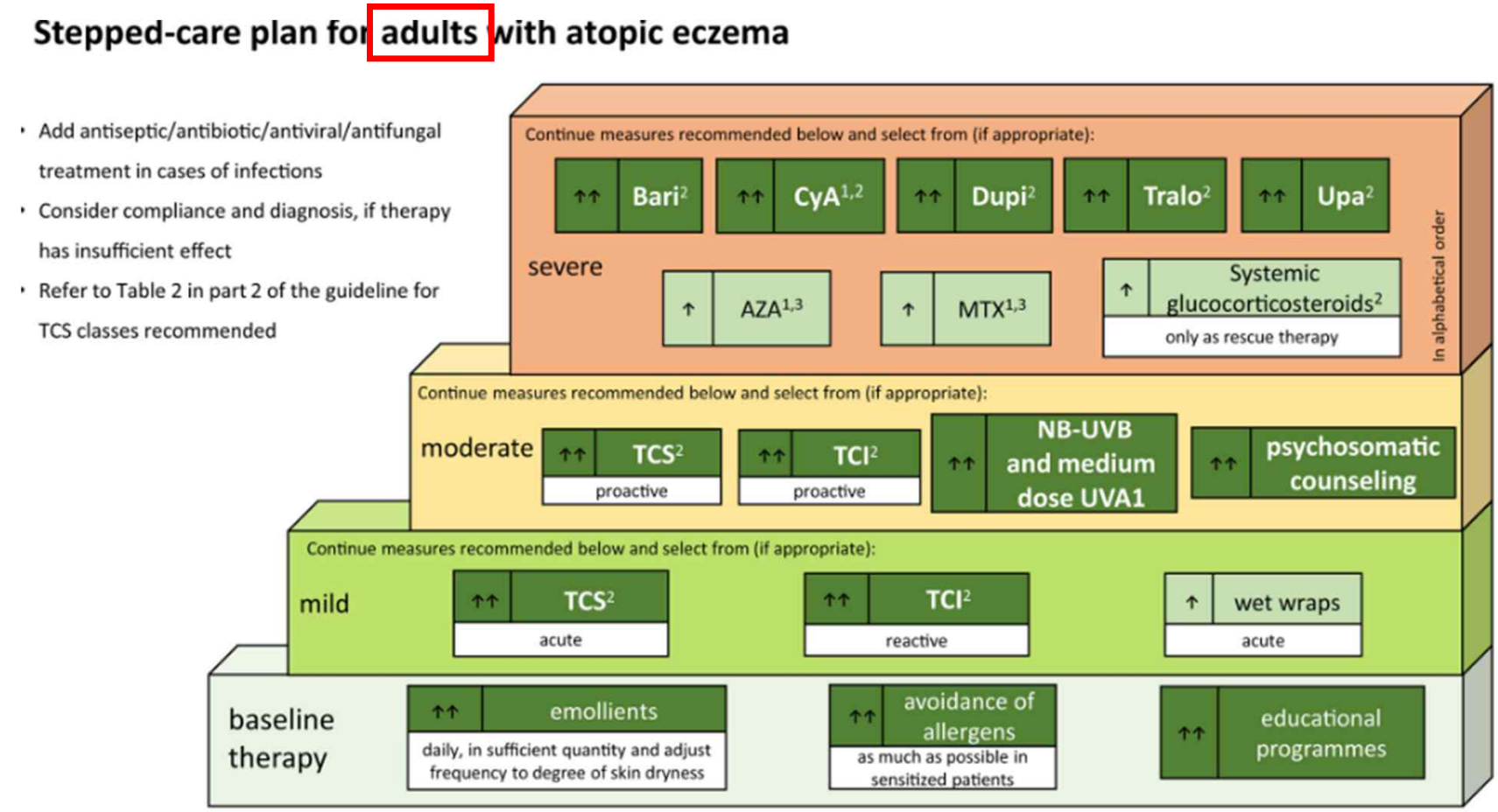
그림 1. 아토피피부염의 치료알고리즘.



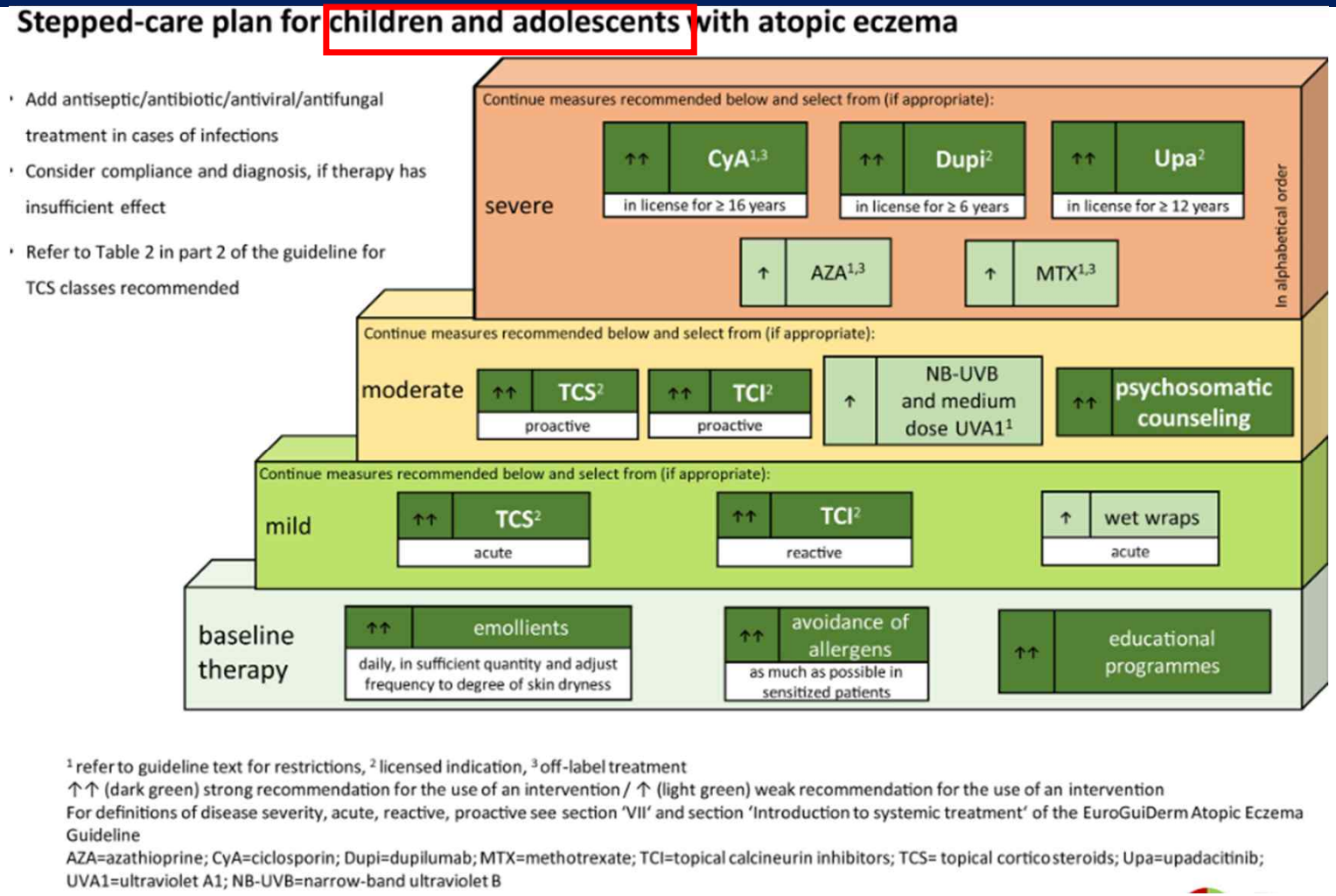
tailored treatment of atopic dermatitis (AD).

Kim JE et al. Ann Dermatol 2015;27(5):578~592

아토피피부염의 치료 – European guideline



아토피피부염의 치료 – European guideline



[1] refer to guideline text for restrictions, [2] licensed indication, [3] off-label treatment
↑↑ (dark green) strong recommendation for the use of an intervention / ↑ (light green) weak recommendation for the use of an intervention
For definitions of disease severity, acute, reactive, proactive see section 'VII' and section 'Introduction to systemic treatment' of the EuroGuiDerm Atopic Eczema Guideline
AZA=azathioprine; CyA=ciclosporin; Dupi=dupilumab; MTX=methotrexate; TCI=topical calcineurin inhibitors; TCS= topical corticosteroids; Upa=upadacitinib; UVA1=ultraviolet A1; NB-UVB=narrow-band ultraviolet B

아토피피부염의 치료 – European guideline

	Conventional systemic treatments			Biologics		JAK-inhibitors		Rescue therapy
	Ciclosporin	Methotrexate	Azathioprine	Dupilumab	Tralokinumab	Baricitinib	Upadacitinib	Systemic corticosteroids
Recommendation	↑↑	↑	↑	↑↑	↑↑	↑↑	↑↑	↑
Dose for adults[1]	licensed ≥ 16 years standard dosage adults: 2.5-5 mg/ kg per day in two single doses	off-label; commonly used dosage adults: initial dose: 5-15 mg/ per week; maximum dose: 25 mg/ week	off-label; commonly used dosage adults: 1-3 mg/kg per day	licensed ≥ 6 years; adults: initially 600 mg s.c. day 1 followed by 300 mg Q2W	licensed for adults; initially 600 mg s.c. day 1 followed by 300 mg Q2W; consider Q4W dosing at week 16 in those achieving clear or almost clear skin	licensed for adults; dosage adults: 4 mg per day, reduction to 2 mg per day possible, depending on treatment response	licensed ≥ 12 years; dosage adults: 15 or 30 mg per day based on individual patient presentation; age ≥ 65: 15 mg per day; the lowest effective dose for maintenance should be considered	general licence for adults and children; dosage maximum: 1 mg/kg per day
Time to response (weeks)[2]	1-2	8-12	8-12	4-6	4-8	1-2	1-2	1-2
Time to relapse (weeks, based on expert experience)[2]	<2	>12	>12	>8	>8	<2	<2	<2
Monitoring	complete blood count, renal and liver profile, blood pressure,	complete blood count, renal and liver profile, PIIINP if available, screen for chronic infections	complete blood count, renal and liver profile, TPMT activity if available, screen for chronic infections	not required	not required	complete blood count, lipid profile, liver profile	complete blood count, lipid profile, liver profile	not required for short-term treatment, consider blood glucose and testing for adrenal gland suppression with high doses/ longer-term treatment
Selection of most relevant adverse events	serum creatinine↑, blood pressure ↑	nausea, fatigue, liver enzymes ↑, myelotoxicity	gastrointestinal disturbances, idiosyncratic hypersensitivity reactions, hepatotoxicity, myelotoxicity	Conjunctivitis, upper respiratory tract infections, arthralgia	upper respiratory tract infections; conjunctitivitis	upper respiratory tract infections, increase in LDL cholesterol; thrombocytosis, nausea and abdominal pain herpes virus infections, acne	upper respiratory tract infections, acne; headache, anaemia and neutropenia, CK elevation, increase in LDL cholesterol, nausea and abdominal pain herpes virus infections	skin atrophy, weight gain, sleep disturbance, mood changes, hyperglycaemia or new onset diabetes, peptic ulcers/ gastritis, osteoporosis

아토피피부염의 치료 – EASI score

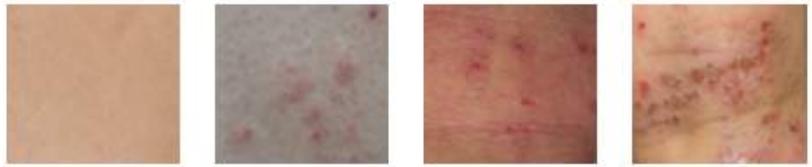
Erythema

○ None = 0 ○ Mild = 1 ○ Moderate = 2 ○ Severe = 3

Edema

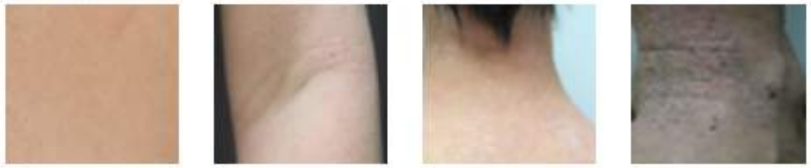
○ None = 0 ○ Mild = 1 ○ Moderate = 2 ○ Severe = 3

Excoriation



○ None = 0 ○ Mild = 1 ○ Moderate = 2 ○ Severe = 3

Lichenification



○ None = 0 ○ Mild = 1 ○ Moderate = 2 ○ Severe = 3

Region score

% involvement	0	1-9%	10-29%	30-49%	50-69%	70-89%	90-100%
Region score	0	1	2	3	4	5	6
	○	○	○	○	○	○	○

아토피피부염 산정특례 조건

· **성인(만 18세이상) 및 청소년(만 12세~만 17세)**

3년 이상 증상이 지속되는 만성 중증 아토피피부염 환자로서 다음의 1), 2) 항 모두 충족

1) **1차 치료제로 국소치료제(중등도 이상의 TCS or TCI)를 4주 이상** 투여하였음에도 적절히 조절되지 않고, 이후 **전신 면역억제제(Cyclosporine 또는 Methotrexate)를 3개월 이상 투여하였음에도** 반응 (EASI 50%이상 감소)이 없거나 부작용 등으로 사용할 수 없는 경우

* 산정특례 등록일 6개월 이내에 국소치료제 및 전신 면역억제제 투여 이력이 확인되어야 함.

2) 산정특례 **등록 전 EASI 23** 이상

아토피피부염 산정특례 조건

· 소아(만 11세 이하)

1년 이상 증상이 지속되는 만성 중증 아토피피부염 환자로서 다음의 1), 2)항 모두 충족

1) 1차 치료제로 **국소치료제(중등도 이상의 TCS or TCS)를 4주 이상** 투여하였음에도 적절히 조절되지 않거나 부작용 등으로 사용할 수 없는 경우

* 산정특례 등록일 4개월 이내에 국소치료제 투여 이력이 확인되어야 함.

2) 산정특례 등록 전 **EASI 21 이상**

* **임상 사진 제출 필수**: EASI 점수 측정 시 중증도 판단을 위한 환부사진이 확인되어야 함.

아토피피부염 약제 급여 조건

1) 성인 및 청소년 (산정특례 조건과 동일)

3년 이상 증상이 지속되는 성인(만 18세 이상) 및 청소년(만 12세-만 17세) 만성 중증 아토피피부염 환자

가) 1차 치료제로 국소치료제(TCI or TCS)를 4주 이상 투여하였음에도 적절히 조절되지 않고, 이후 전신 면역억제제(Cyclosporine 또는 Methotrexate)를 3개월 이상 투여하였음에도 반응(EASI(Eczema Area and Severity Index) 50%이상 감소)이 없거나 부작용 등으로 사용할 수 없는 경우

* 동 약제 투약개시일 6개월 이내에 국소치료제 및 전신 면역억제제 투여이력이 확인되어야 함.

나) 동 약제 투여시작 전 EASI 23 이상

아토피피부염 약제 급여 조건

2) 소아 (만 6세-만 11세) (산정특례 조건과 동일)

1년 이상 증상이 지속되는 소아(만 6세-만 11세) 만성 중증 아토피피부염 환자로서 다음의 조건을 모두 만족하는 경우

가) 1차 치료제로 국소치료제(중등도 이상의 TCS or TCI)를 4주 이상 투여하였음에도 적절히 조절되지 않거나, 부작용 등으로 사용할 수 없는 경우

* 동 약제 투약개시일 4개월 이내에 국소 치료제 투여이력이 확인되어야 하며, 국소치료제 투여 시점에 EASI 21 이상이어야 함.

나) 동 약제 투여시작 전 EASI 21 이상
* 임상 사진 제출 필수: EASI 점수 측정 시 중증도 판단을 위한 환부사진이 확인되어야 함

사이토카인 (Cytokines)

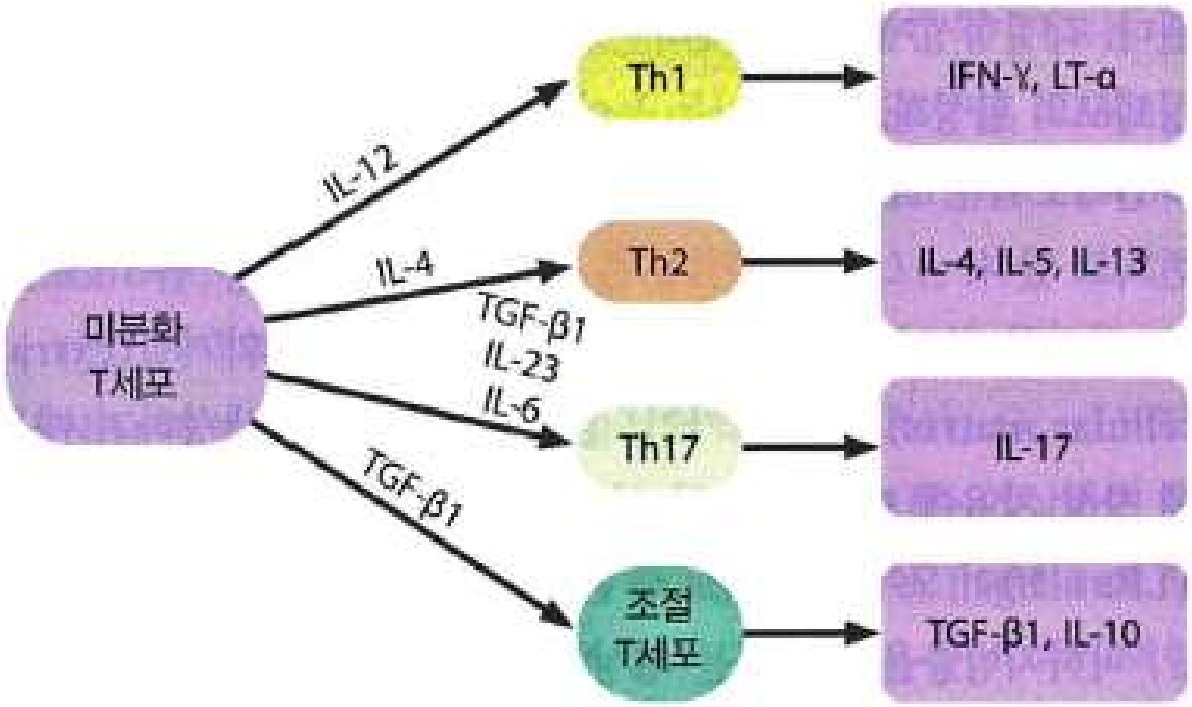
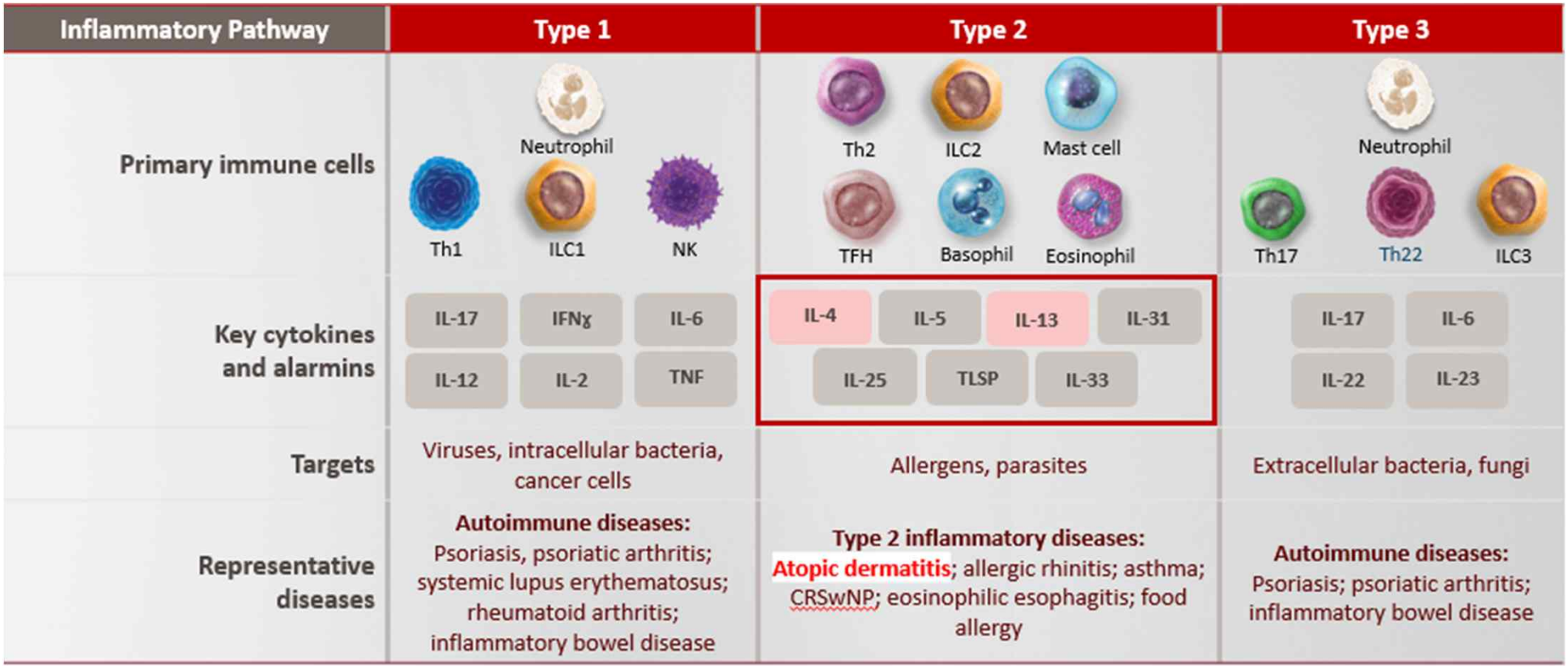


그림 4-1 ▸ CD4 보조 T세포의 분화와 관련 사이토카인.

Reference: 피부과학 7판

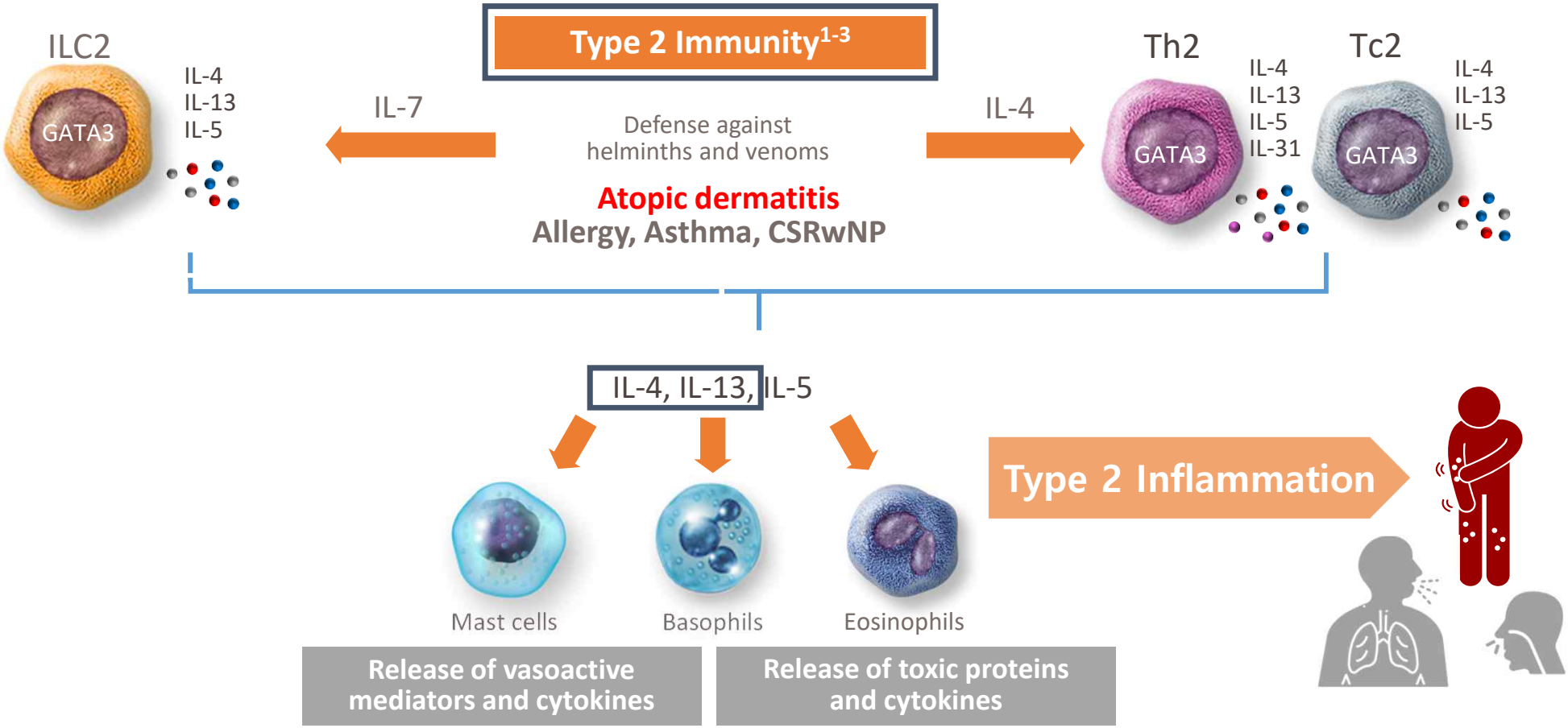
Three Types of Immunity

IL-4 and IL-13 as Key Players of the Type 2 Immune Response



This figure is a simplified representation of some of the key drivers of immune response. It is not intended to serve as an exhaustive list. CRSwNP, chronic rhinosinusitis with nasal polyps; IL, interleukin; Th2, T helper type 2; TSLP, thymic stromal lymphopoietin. 1. Annunziato F, et al. J Allergy Clin Immunol. 2015;135(3):626–635; 2. Cosmi L, et al. Eur J Immunol. 2019. 49:1334–1343; 3. Sahoo A, et al. Cytokine Growth Factor Rev. 2016;30:29–37; 4. Hulse KE. Curr Allergy Asthma Rep. 2016;16:1; 5. Kaiko GE et al. Immunology. 2008;123:326–338.

Common Role of Type 2 Inflammation

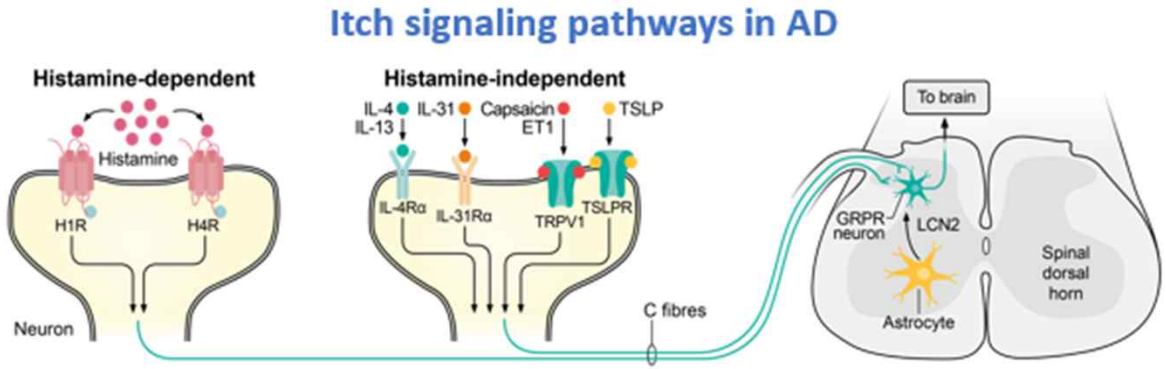


Pruritus

1. The sensation of **itch is mediated** by the interplay between:
- Epidermal cells
- Cells of the immune system
- The peripheral and central nervous system (both neurons and glia)

2. **Different types of itch exist**
e.g. chemical and mechanical

Chemical itch can be further subdivided into histaminergic vs. non-histaminergic
Itch pathways are associated with various receptors on cutaneous nerve fibers in the periphery
Chronic pruritus is primarily induced by the non-histaminergic pathway



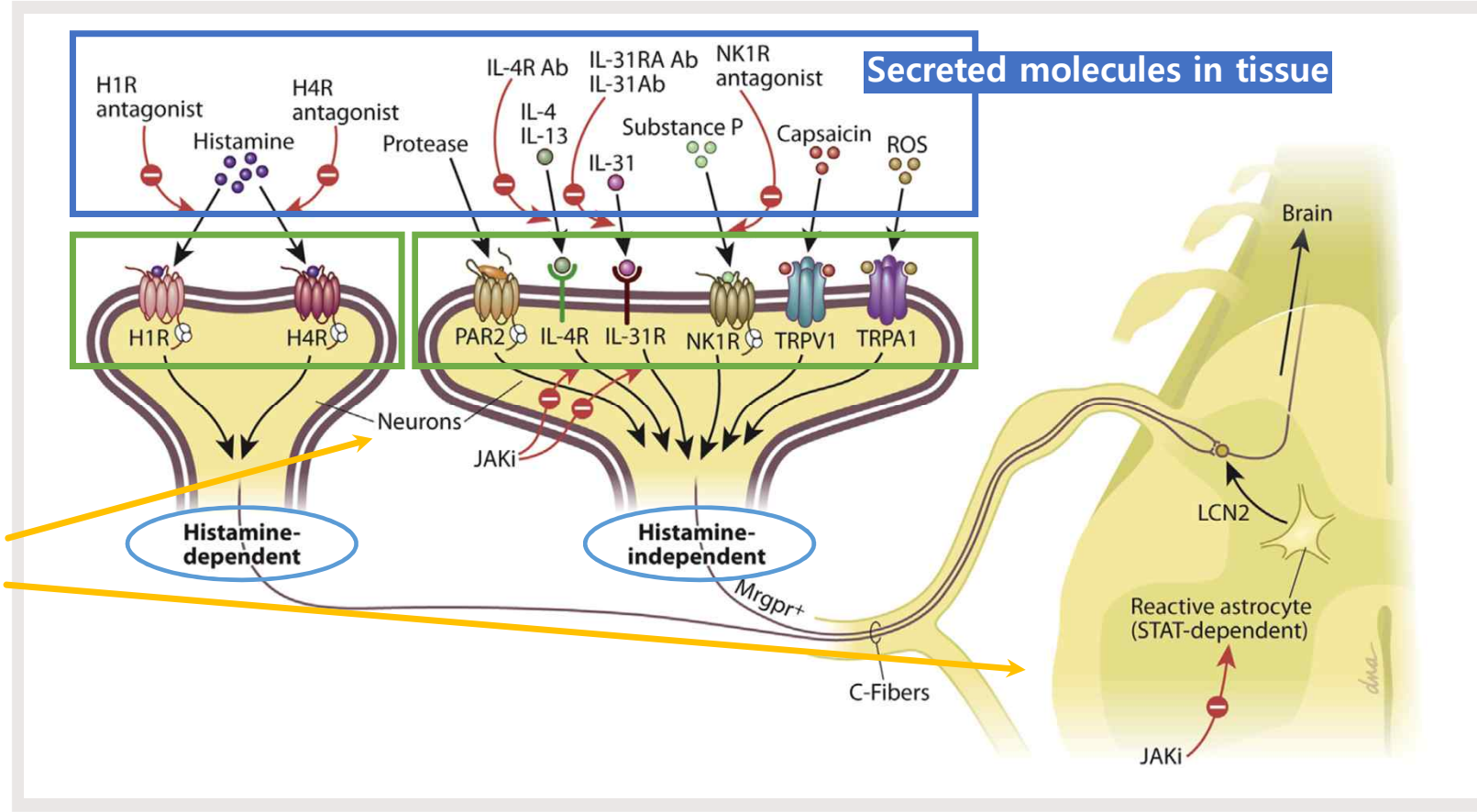
The mechanism of Pruritus

Chemical mediators (including cytokines)

e.g. histamine, Interleukin 31 (IL-31), IL-4/IL-13 (facilitating), TSLP, substance P (SP)

Receptors and Ion channels

Activation of neurons in peripheral and central nervous system



- Figure adapted from: Paller AS, et al. J Allergy Clin Immunol. *2017;140:633-43.*

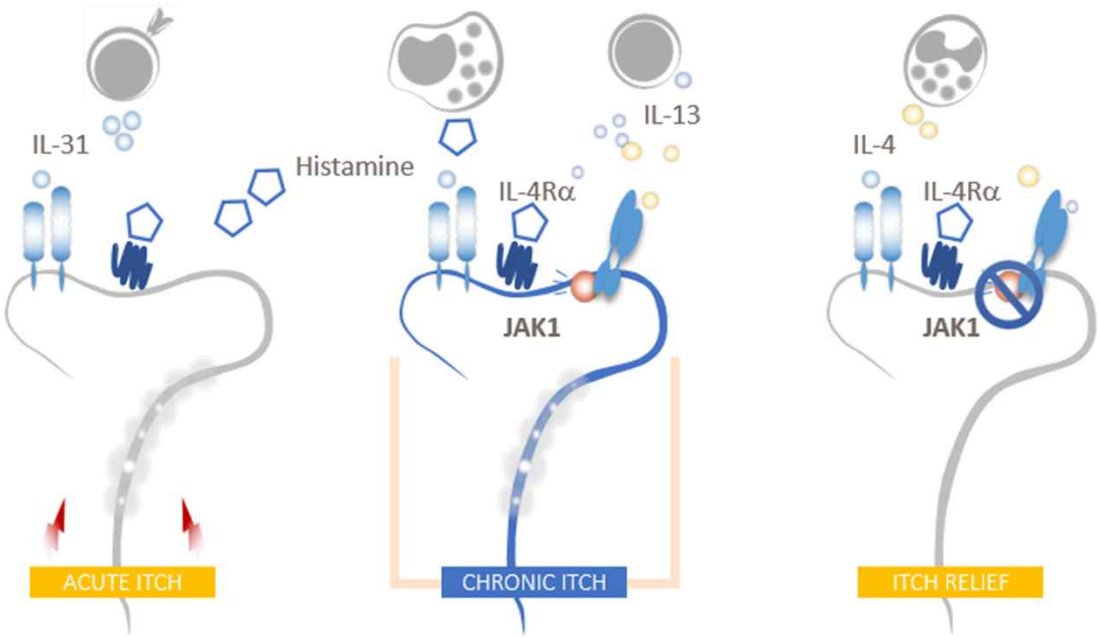
1. Paller AS, et al. J Allergy Clin Immunol. 2017;140:633-43.

Role of IL-4 and IL-13 in itch induction

- In AD, the type 2 cytokines IL-4, IL-5 and IL-13 are known to drive skin inflammation
- Recent studies have dissected the critical role of **IL-4 and IL-13 in the pathogenesis of chronic itch**

  Mice that overexpress IL-4 or IL-13 in the skin develop AD-like disease and robust chronic itch
- IL-4 and IL-13 sensitize the sensory neurons to pruritogens
- This sensitizing effect can be blocked by JAK inhibitors

  Knocking out IL-4Rα in mouse neurons leads to a significant reduction in scratching behavior, as well as in skin inflammation



IL-4 and IL-13 are not directly pruritogenic

- Surprisingly, **unlike IL-31, high doses of either IL-4 or IL-13 did not elicit acute itch**
- Thus, these findings suggest that the Type 2 cytokines IL-4 or IL-13 do not function as potent acute pruritogens, despite activating itch-sensory neurons
- Sensory neurons are directly activated by the classical immune signaling molecules IL-4 and IL-13
- Surprisingly, **rather than triggering acute itch, activation of neuronal IL-4Rα sensitizes sensory neurons to multiple other pruritogens**

아토피피부염의 치료 - Dupilumab

- 성인(만 18세 이상)

이 약은 초회 용량으로 600 mg (300 mg을 다른 투여부위로 연속 2회) 투여하고, 이후 유지 용량으로 300 mg을 2주 간격으로 피하투여한다.

- 소아(만 6-만 11세) 및 청소년(만 12-만 17세)

이 약은 체중에 따라 다음 표에 따라 피하투여한다.

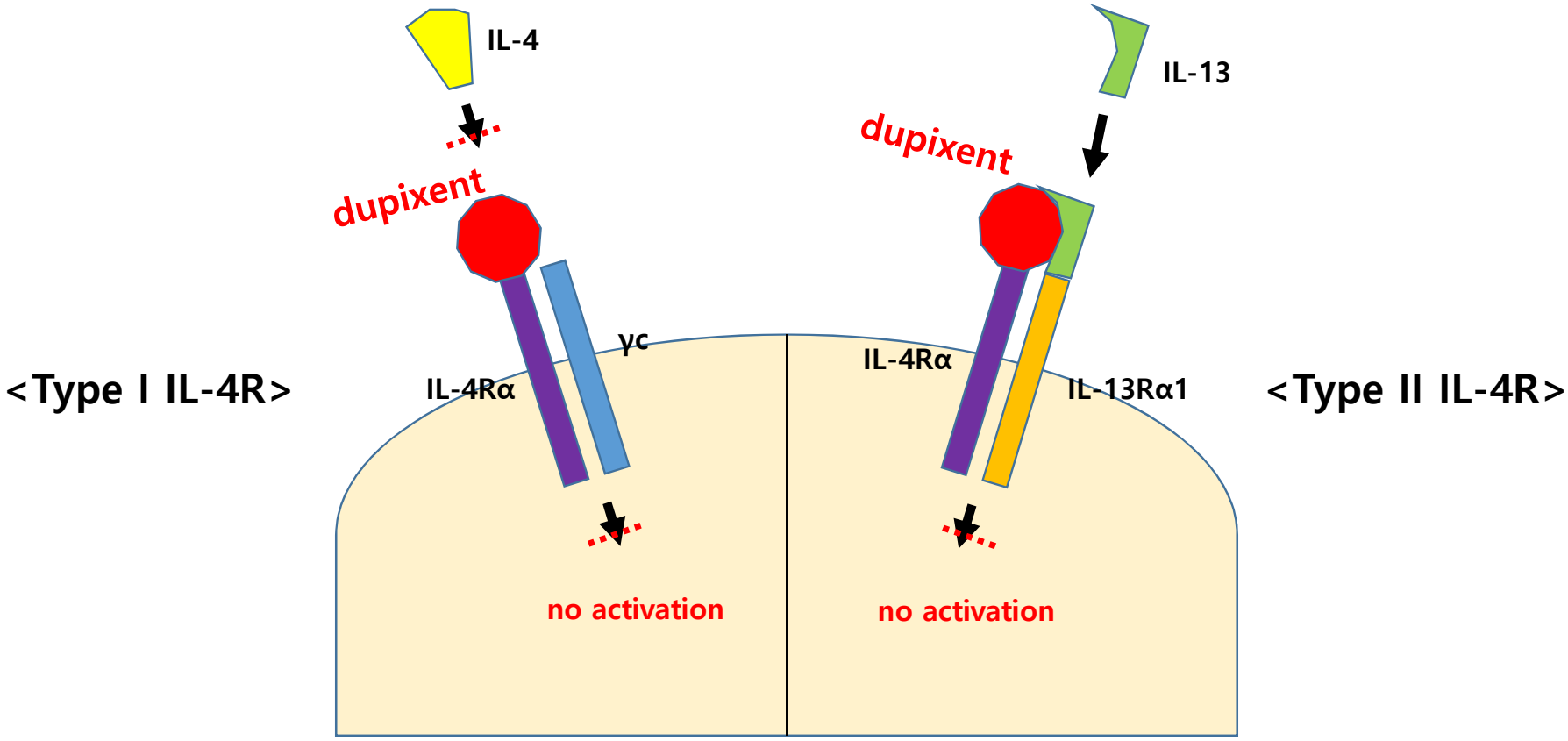
몸무게	초회 용량	유지 용량
15 kg 이상 30 kg 미만	600 mg(300 mg 2회 투여)	300 mg(4주 간격)
30kg 이상 60 kg 미만	400 mg(200 mg 2회 투여)	200 mg(2주 간격)
60 kg 이상	600 mg(300 mg 2회 투여)	300 mg(2주 간격)

- 소아(만 6개월-만 5세)

이 약은 체중에 따라 다음 표에 따라 피하투여한다.

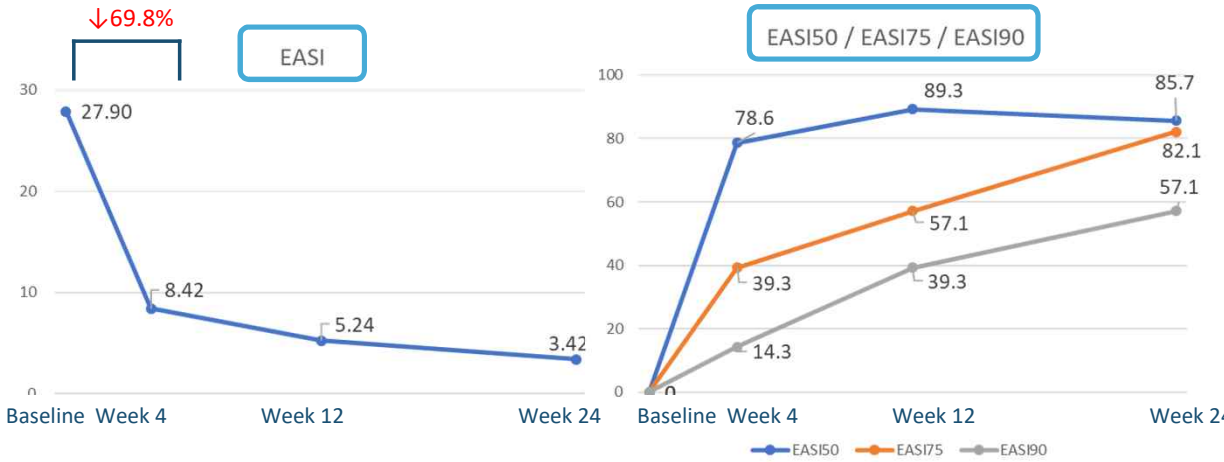
몸무게	초회 용량	유지 용량
5kg 이상 15kg 미만	200 mg(200 mg 1회 투여)	200mg (4주 간격)
15kg 이상 30kg 미만	300 mg(300 mg 1회 투여)	300mg (4주 간격)

아토피피부염 Atopic dermatitis – dupixent(dupilumab)



Efficacy of 6-Months Dupilumab Treatment in Children Aged 6-11 years with Moderate-to-Severe Atopic Dermatitis in South Korea: Interim Analysis of Multicenter Prospective Observational Study (KAPARD 2022, best oral presentation award)

Variables	N=28
Male : Female	19 : 9
Age (mean ± SD)	9.18±1.47
Onset age (mean ± SD)	2.82±2.60
IGA	IGA 3 (n=4) IGA 4 (n=24)
Coexisting other allergic diseases	23 (82.1%)
Asthma	8 (28.6%)
Allergic rhinitis	22 (78.6%)
Allergic conjunctivitis	13 (46.4%)
Food allergy	14 (50%)
Family history of allergic diseases	
Atopic dermatitis	11 (39.3%)
Asthma	7 (25.0%)
Allergic rhinitis	22 (78.6%)
Food allergy	7 (25.0%)



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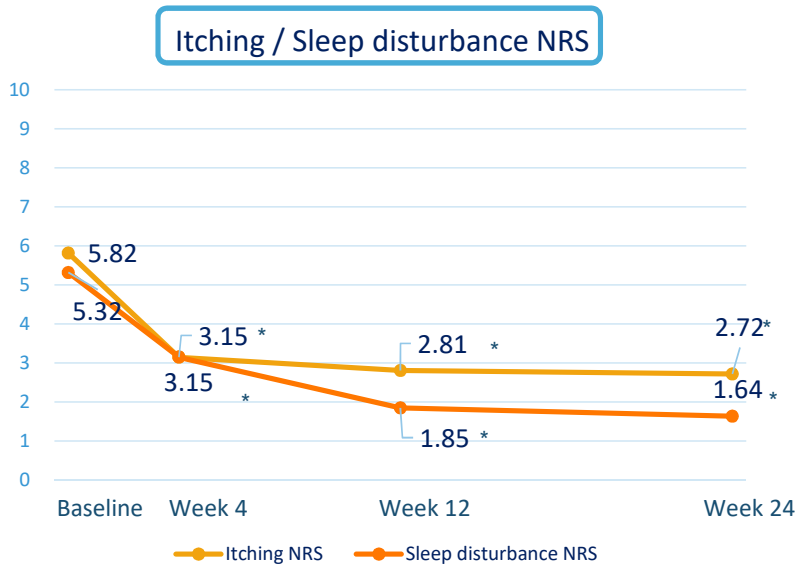
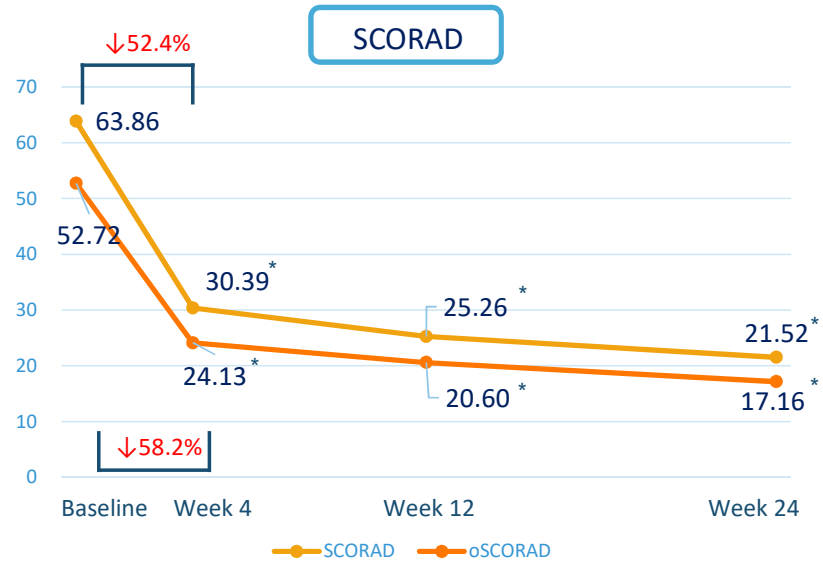


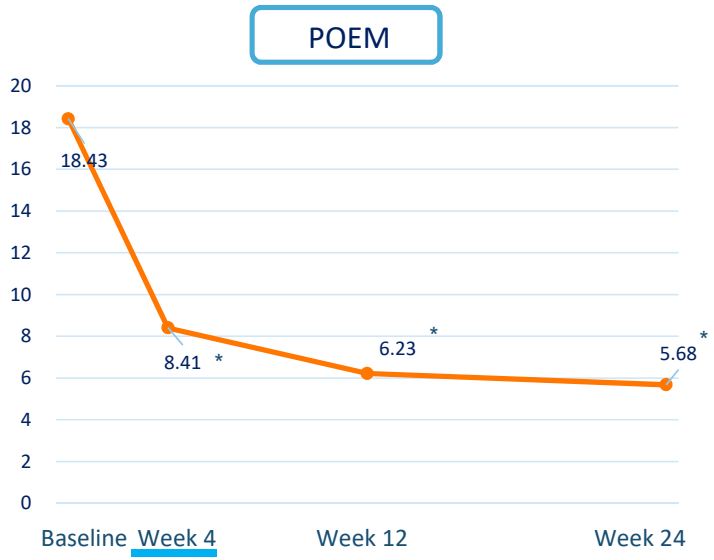


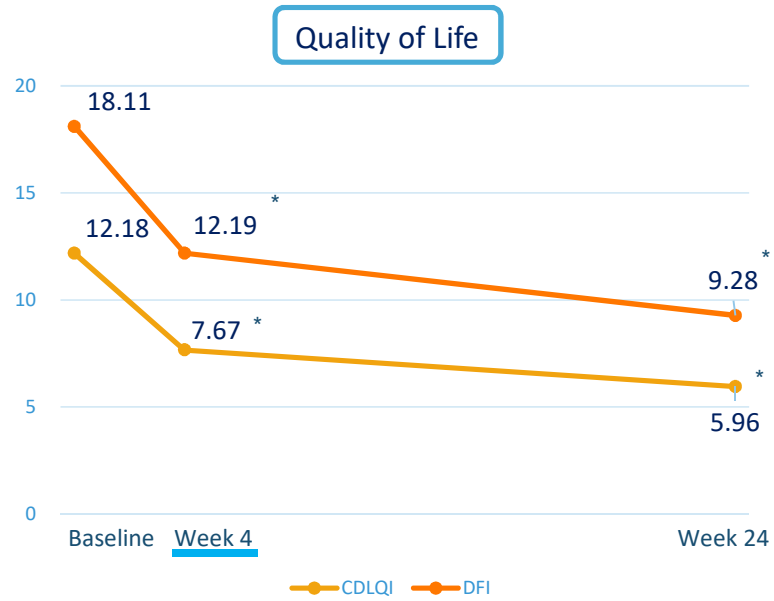
Efficacy of 6-Months Dupilumab Treatment in Children Aged 6-11 years with Moderate-to-Severe Atopic Dermatitis in South Korea: Interim Analysis of Multicenter Prospective Observational Study (KAPARD 2022, best oral presentation award)

Adverse events

- Conjunctivitis ; 2 cases (7.1%)
- Injection site urticaria ; 2 cases (7.1%)
- Angioedema (around eyes) ; 1 case (3.5%)
- Hair loss ; 1 case (3.5%)

Efficacy of 6-Months Dupilumab Treatment in Children Aged 6-11 years with Moderate-to-Severe Atopic Dermatitis in South Korea: Interim Analysis of Multicenter Prospective Observational Study (KAPARD 2022, best oral presentation award)





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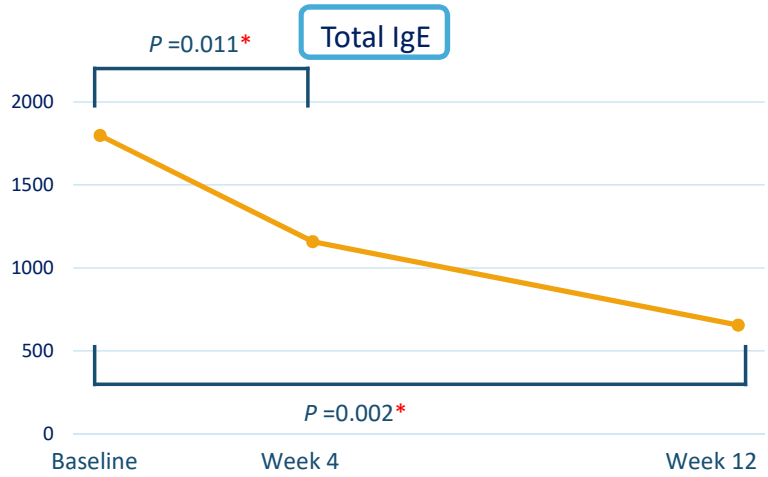

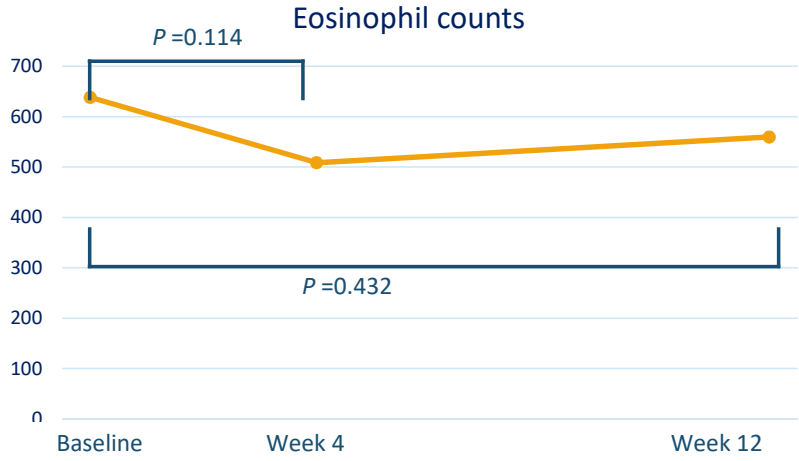

Dupilumab Indication & Reimbursement Criteria in Korea

DUPIXENT Korea AD Indication[1]

treatment of patients aged 6 months and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

DUPIXENT Korea Reimbursement Criteria [2,3]

소아 (만 6세-11세)	성인 및 청소년 (만 12세 이상)
1년 이상 증상이 지속되는 만성 중증 아토피피부염 환자로서 다음의 조건을 모두 만족하는 경우 - 1차 치료제로 국소치료제(중등도 이상의 TCS 또는 TCI)를 4주 이상 투여하였음에도 적절히 조절되지 않거나, 부작용 등으로 사용할 수 없는 경우 * 동 약제 투약개시일 4개월 이내에 국소 치료제 투여이력이 확인되어야 하며, 국소치료제 투여 시점에 EASI 21점 이상이어야 함 - 동 약제 투여시작 전 EASI 21 이상 * 임상 사진 제출 필수: EASI 점수 측정 시 중증도 판단을 위한 환부 사진이 확인되어야 함	3년 이상 증상이 지속되는 만성 중증 아토피피부염 환자로서 다음의 조건을 모두 만족하는 경우 - 1차 치료제로 국소치료제(중등도 이상의 TCS 또는 TCI)를 4주 이상 투여하였음에도 적절히 조절되지 않고, 이후 전신 면역억제제(Cyclosporine 또는 Methotrexate)를 3개월 이상 투여하였음에도 반응(EASI 50%이상 감소) 이 없거나 부작용 등으로 사용할 수 없는 경우 * 동 약제 투약개시일 6개월 이내에 국소치료제 및 전신면역억제제 투여이력이 확인되어야 함. - 동 약제 투여시작 전 EASI 23 이상

1. 듀피젠트® 프리필드주 200/300 밀리그램 제품설명서 (2021.03.09). 2. 보건복지부 고시 제2019-341호.
3. 보건복지부 고시 제2020-308호 (2020.12.24.)「본인일부부담금 산정특례에 관한 기준」

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Dupilumab Indication & Reimbursement Criteria in Korea

DUPIXENT Korea Reimbursement Criteria [2,3]

급여 유지 평가 방법

- 동 약제를 14주간 투여 후 16주째 평가하여 EASI가 75%이상 감소한 경우 추가 6개월의 투여를 인정함.
- 이후에는 지속적으로 6개월마다 평가하여 최초 평가결과가 유지되면 지속적인 투여를 인정함

기타 주의 사항

- Dupilumab 주사제와 JAK 억제제 사이의 교체투여는 인정하지 않음.
- 원내처방을 원칙으로 하며, 퇴원 시 및 외래에서의 1회 처방기간은 최대 4주 분까지로 함.
  - 단, 최초 투약일로부터 **24주 이후**에 안정된 질병활동도를 보이고 부작용이 없는 환자의 경우에는 최대 **8~12주분까지** 인정함

- 동 약제는 아토피 관련 진료과(피부과, 알레르기내과, **소아알레르기호흡기**) 전문의가 처방하여야 하며, 최초 투여 시 투여 대상 및 지속투여 시 반응평가에 대한 객관적 자료(약제투여 과거력, EASI 산출근거, 환부 사진 등)를 반드시 제출하여야 함

1. 듀피젠트® 프리필드주 200/300 밀리그램 제품설명서 (2021.03.09). 2. 보건복지부 고시 제2019-341호.
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아토피피부염의 치료- Jak inhibitor

1. Rinvoq (Upadacitinib)

- Dupixent 와 급여조건 동일
- 3년 이상 증상이 지속되는 **성인(만 18세 이상) 및 청소년(만 12세-만 17세)** 만성 중증 아토피피부염 환자
- **다만, 65세 이상 환자, 심혈관계 고위험군 환자, 악성 종양 위험이 있는 환자는 제외함.**

2. Olumiant (Baricitinib)

- Dupixent 와 급여조건 동일
- 3년 이상 증상이 지속되는 **성인 만성 중증 아토피 피부염 환자**
- **다만, 65세 이상 환자, 심혈관계 고위험군 환자, 악성 종양 위험이 있는 환자는 제외함.**

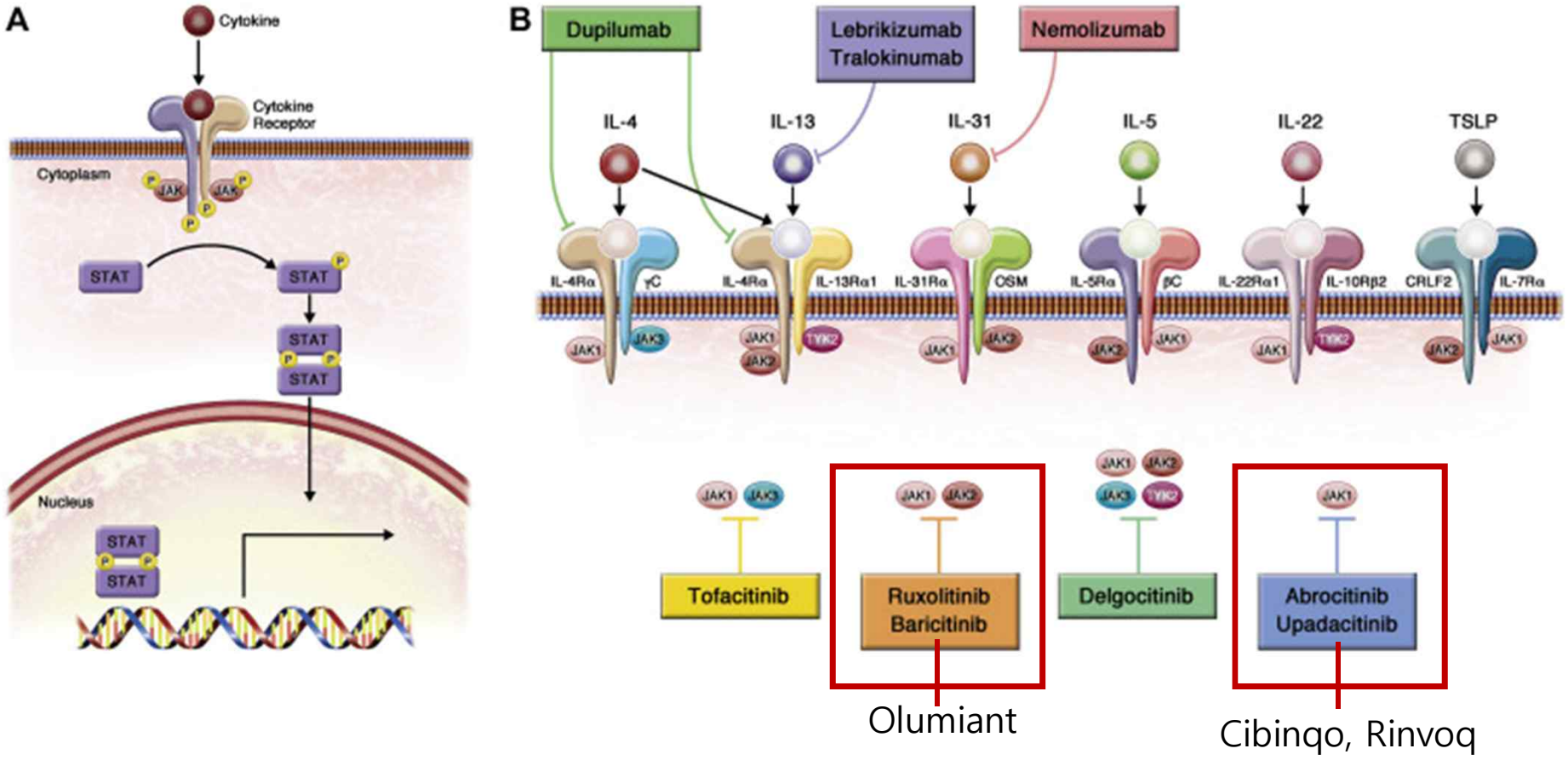
아토피피부염의 치료- Jak inhibitor

3. Cibinqo (Abrocitinib)

- Dupixent 와 급여조건 동일
- 3년 이상 증상이 지속되는 **성인(만 18세 이상) 및 청소년(만 12세-만 17세)** 만성 중증 아토피피부염 환자
- **다만, 65세 이상 환자, 심혈관계 고위험군 환자, 악성 종양 위험이 있는 환자는 제외함.**

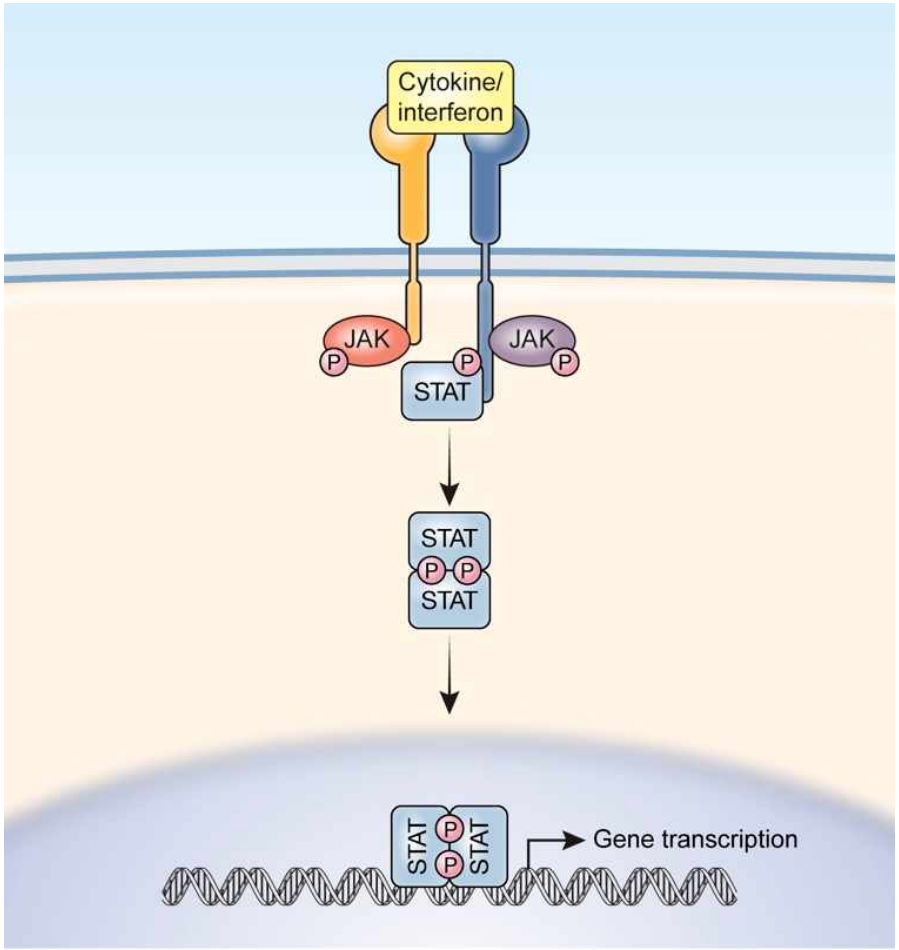
JAK 억제제 간 교체투여 및 dupilumab 주사제와 JAK 억제제 사이의 교체투여는 인정하지 않음

아토피피부염의 치료- Jak inhibitor



Jak Inhibitor

Type I/II cytokine signaling

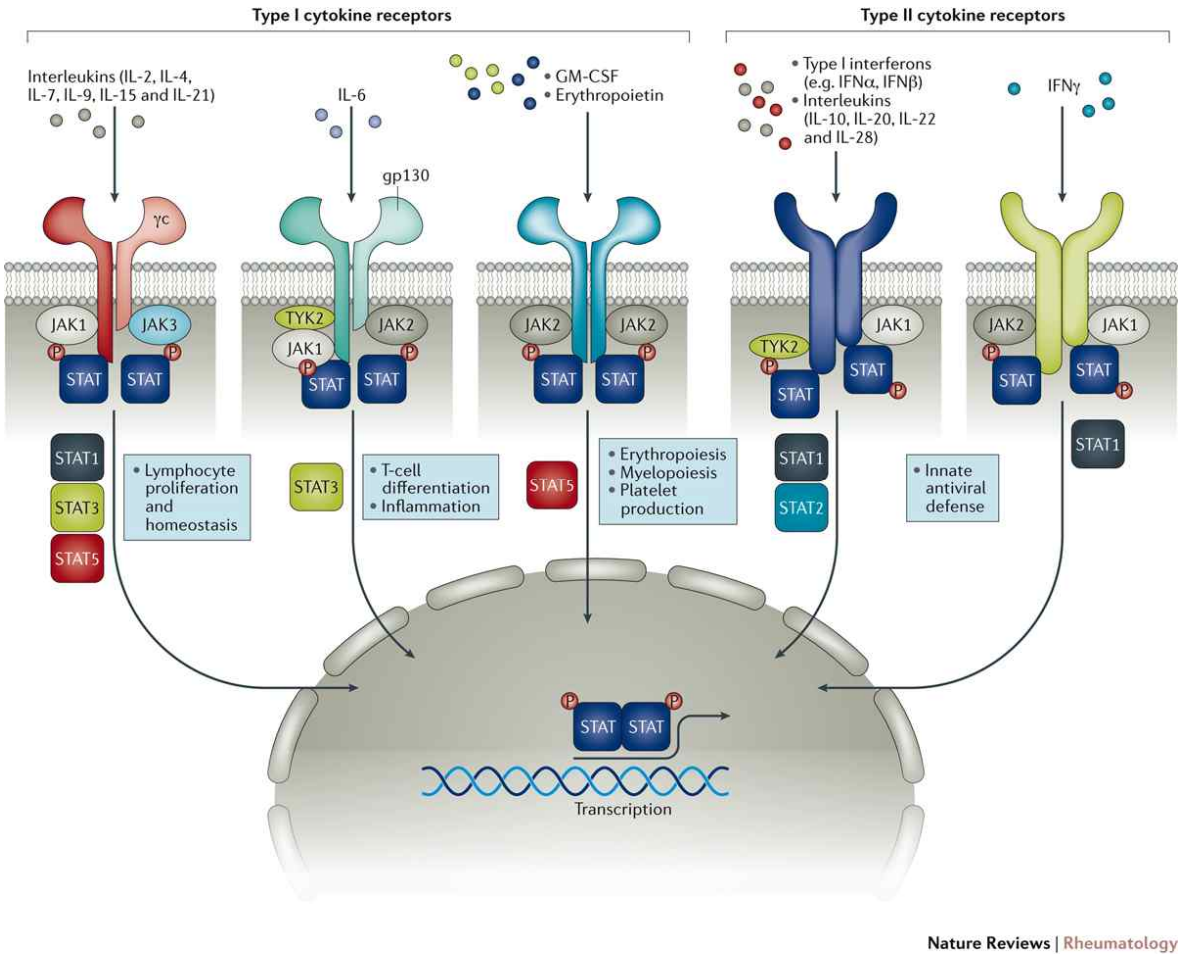


Rapid membrane to nucleus signaling:

1. Cytokines bind transmembrane receptors that are associated with JAKs
2. Binding activates JAKs
3. JAKs phosphorylate receptors
4. STATs bind receptors
5. JAKs phosphorylate STATs
6. STATs dimerize
7. STATs translocate to the nucleus
8. STATs bind DNA and regulate transcription

Jak Inhibitor

JAKS work in pairs

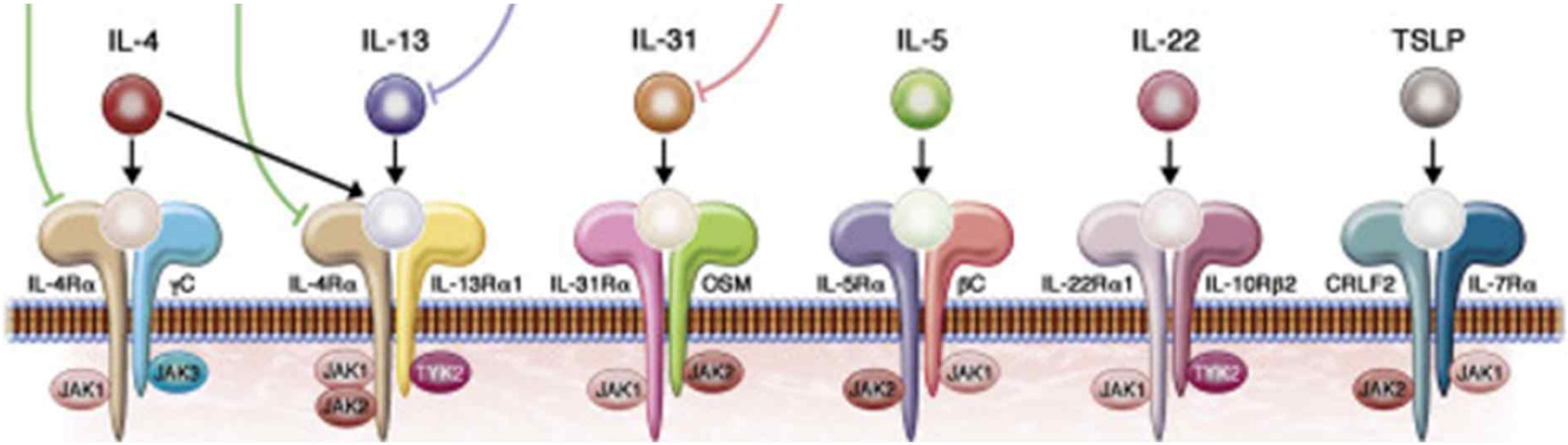


- Four JAKs: JAK1, JAK2, JAK3, Tyk2
- JAKs work in pairs
- Different receptors bind different JAKs
- Different immunomodulatory signals are generated

Once a cytokine receptor is activated,
JAKs trigger intracellular signal transduction cascades that regulate a **variety of processes depending on the JAK combination**

Jak Inhibitor

Different cytokines drive different aspects of AD pathogenesis



	IL-4	IL-4/IL-13	IL-31	IFNY	IL-22	TSLP
Promotion of inflammation	O	O	O	O		O
Promotion of itching and subsequent scratching	O	O	O		O	O
Skin barrier disruption	O	O			O	
Skin microbiome dysbiosis	O	O				
Epidermal thickening	O				O	

AD pathogenesis is mediated by both JAK-dependent and JAK-independent cytokines

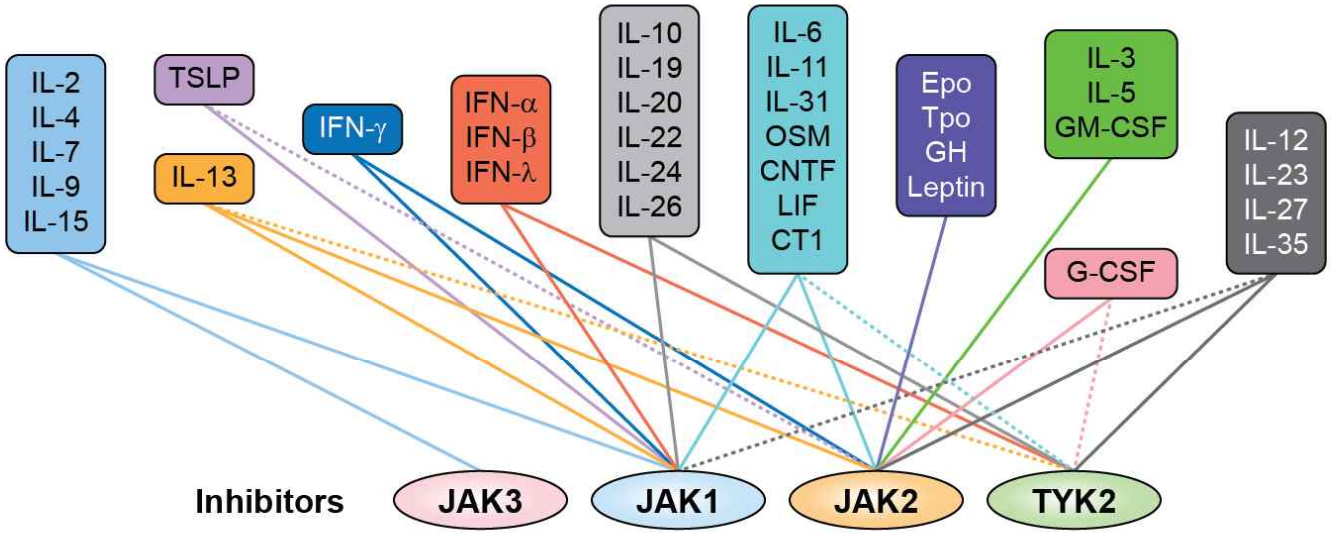
JAK-dependent cytokines	Associated with lesions in	
	Acute AD	Chronic AD
IFNα and IFNβγ		
IL-4	+	
IL-5	+	
IL-6	+	
IL-12		+
IL-13		+
IL-31		+
IL-21	+	
IL-22		
IL-23	+	
TSLP	+	

JAK-independent cytokines	Non-JAK pathways	Associated with	
		Acute AD	Chronic AD
IL-1	NF-κB, JNK-MAPK[9]		+
IL-17C (IL-25)	C/ERBb[2], NF-κB9[10], PI-3K[14]		++
TGF-β	p38-MAPK[12], SMADs[2]		
TNF-α	IκB/NF-κB[2]		
IL-33	NF-κB, ERK1/2, JNK, p38, PI3K/AKT[13]	+	

1. Renert Y, et al. Clin Dermatology. 2017;35:387-397. 2. Schwartz DM, et al. Nat Rev Rheumatol 2016;12:25-36. 3. Brunner PM, et al. Ann Allergy Asthma Immunol. 2018;120(1):34-41. 4. Floudas A, et al. J Immunol. 2017;199(2):707-717. 5. Wang B, et al. J Invest Dermatol. 2017;137(1):95-105. 6. DaSilva-Arnold SC, et al. Arch Dermatol Res. 2018;10(3):197-207. 7. Ruzicka T, et al. NEJM. 2017;376:826-835. 8. Cotter DG, et al JAAD 2018;78: S53-62. 8. Vandeghinste N, et al. JID 2018;138(7):1555-1563. 9. Gómez-García F, et al. Dermatol Ther (Heidelb). 2018;8(2):195-202. 10. Kumar P, et al. Cell Signal. 2014;26(3):528-39. 11. Kao CY, et al. J Immunol. 2005;175(10):6676-85. 12. Lan CC, et al. J Eur Acad Dermatol Venereol. 2014;28(2):204-15. 13. Pinto SM, et al. J Cell Commun Signal. 2018;12(3):615-624.

Jak Inhibitor

FIRST-GEN JAK INHIBITORS TARGET MULTIPLE CYTOKINES

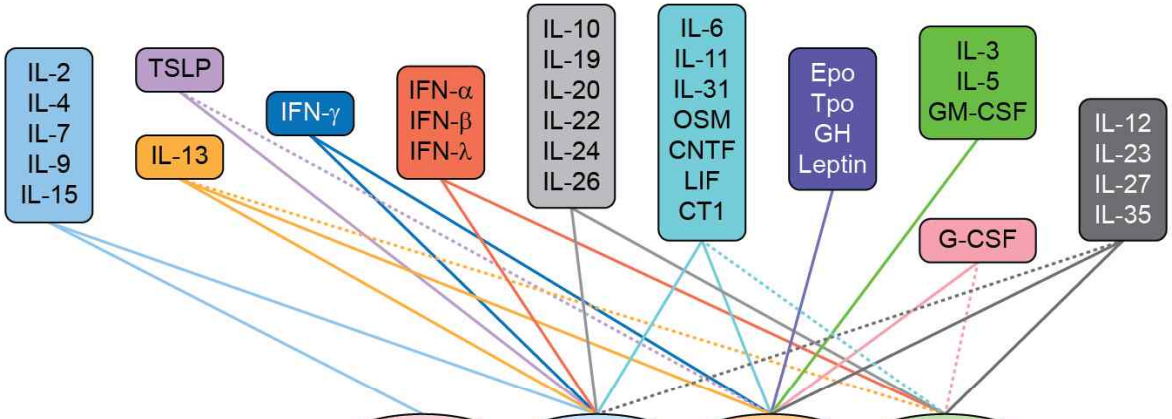


Inhibitors	JAK3	JAK1	JAK2	TYK2
Tofacitinib	×	×	×	
Ruxolitinib		×	×	
Baricitinib		×	×	
Peficitinib	×	×	×	

- Current Jakinibs inhibit multiple JAKs
- Inhibit innate and adaptive immune responses
- cell- and state-specific dependency of given JAK and cytokine incompletely defined

Jak Inhibitor

NEXT-GEN JAK INHIBITORS ARE MORE SELECTIVE



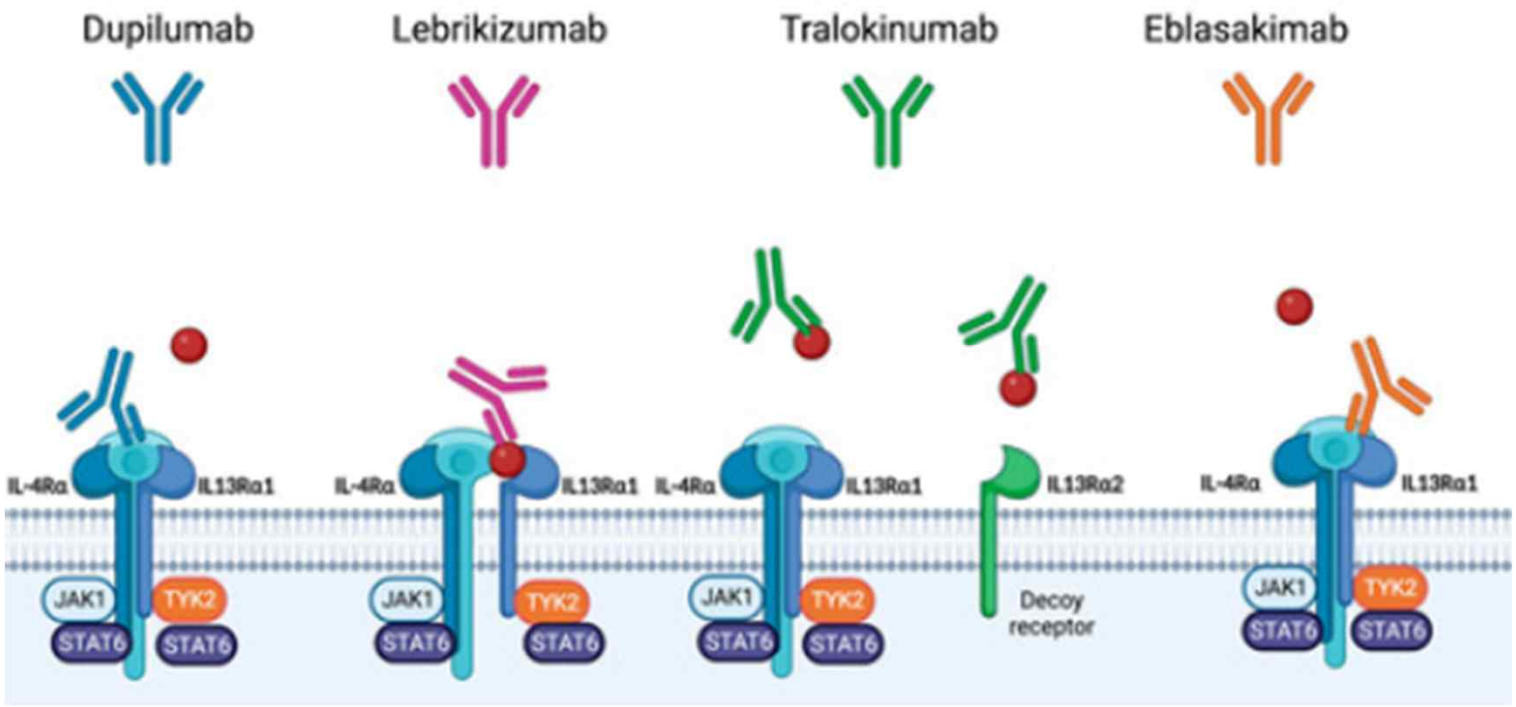
Inhibitors	JAK3	JAK1	JAK2	TYK2
Momelotinib			×	
Fedratinib			×	
Filgotinib		×		
Upacitinib		×		
Itacitinib		×		
PF-06651600	×			
BMS-986165				×
PF-06700841		×		×

JAK Family selectivity profiles

	JAKi	"Selectivity"	Actual
Rinvoq	UPA	JAK1	**JAK1>JAK2>JAK3>Tyk2**
Olumiant	BARI	JAK1/2	**JAK1/2/> JAK3/Tyk2**
	ABRO	JAK1	**JAK1>JAK2>Tyk2>JAK3**
	TOFA	JAK1/3	**JAK1/3> Tyk2/JAK2**

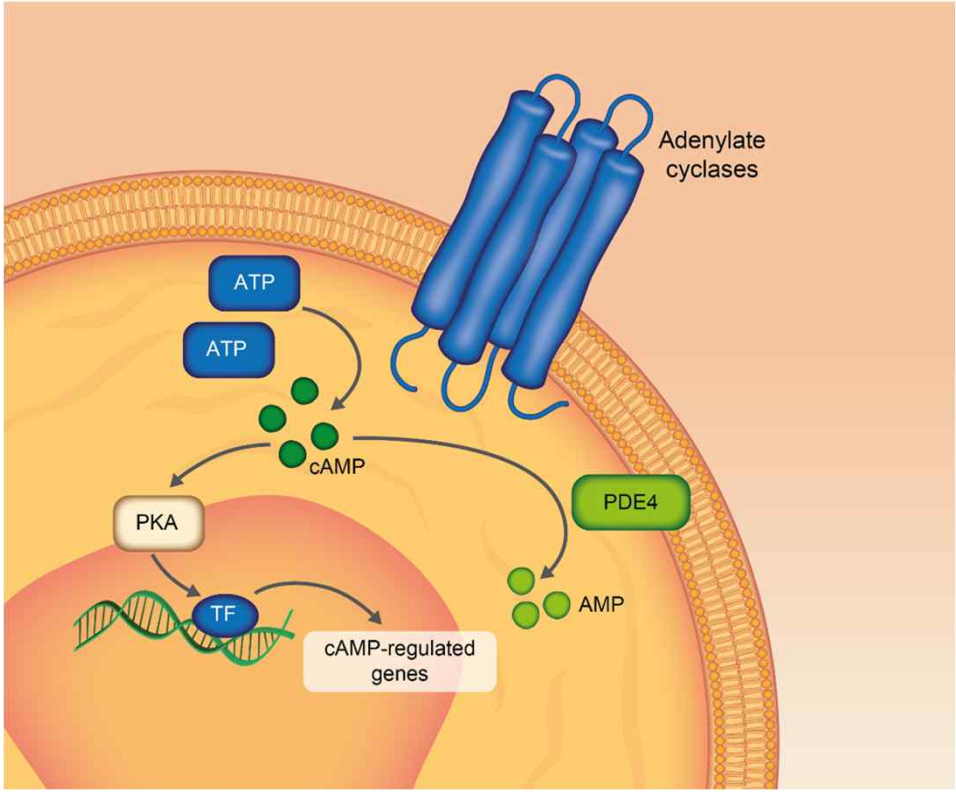
아토피피부염의 치료- IL-13 blocker

IL-13 blocker – Tralokinumab (brand name : Adtralza, LEO pharma)



아토피피부염의 치료- small molecules

1. Phosphodiesterase 4 (PDE4) Inhibitors ; Crisaborole (topical)

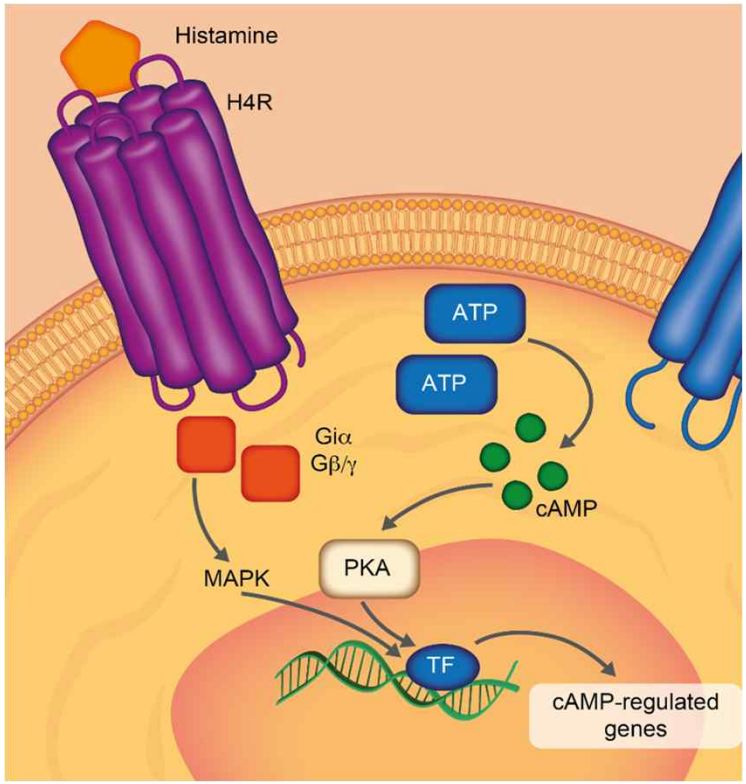


- **High levels and increased activity of PDE4** are found in leukocytes of patients with AD
- PDE4 catalyzes the breakdown of cAMP, a molecule known to downregulate inflammation
- There are four genetically distinct PDE4 subtypes (A–D), with different regulatory behavior and tissue expression patterns
- **Inhibition of PDE4 causes:**

▲ intracellular cAMP levels & anti-inflammatory mediators
▼ proinflammatory mediators

아토피피부염의 치료- small molecules

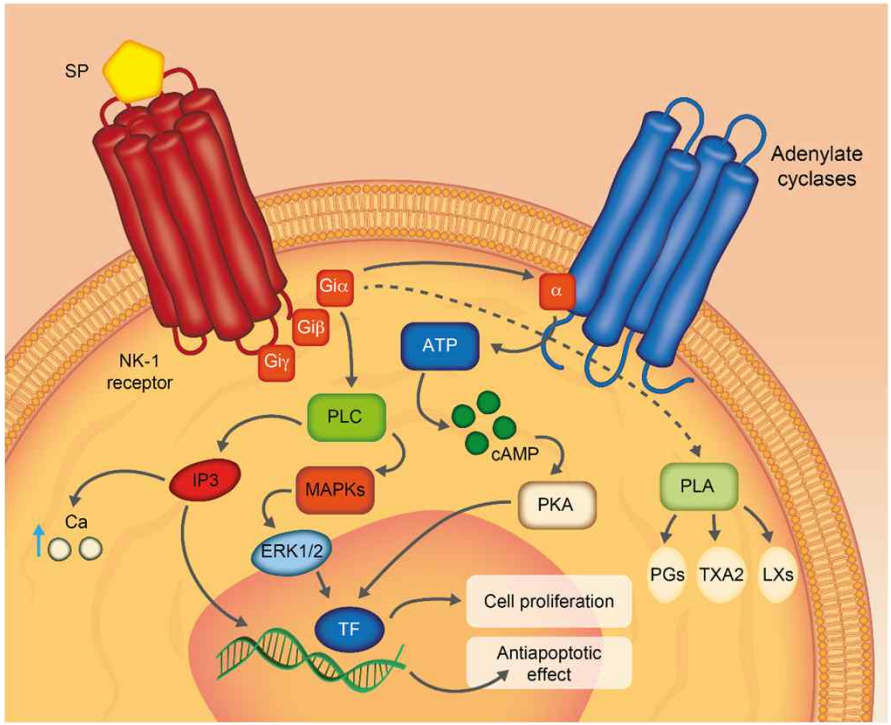
2. Histamine Receptor 4 (H4R)-Targeted treatment



- H4R, one of four histamine receptors, is preferentially expressed on T cells, NK cells, DCs, basophils, eosinophils, and mast cells.
- **Binding of histamine to H4R contributes to chronic inflammation and itching in patients with AD**
- In this patient population, H4R:
  - -Is overexpressed on $CD4^+$ T cells, compared with $CD4^+$ cells from patients without AD
  - -Modulates Th2 cytokine production in LCs
  - -Upregulates IL-31 mRNA in Th2 cells, leading to keratinocyte proliferation

아토피피부염의 치료- small molecules

3. Neurokinin-and Neurokinin-1 Rc. targeted treatment ; Tradipitant (oral), Serlopitant (oral)



The neuropeptide substance P (SP) is a major mediator of pruritus in inflammatory skin conditions, including AD

SP mediates itch and pain via:
-Direct stimulation of spinal neurons
-The release of histamine from skin mast cells
-Expression in dermal fibroblasts of the neurotrophic factor artemin, which is -upregulated in AD skin lesions and stimulates warmth-evoked scratching in mice

SP expression is upregulated in $CD8^+$ T cells of patients with AD

NK1R is expressed across a variety of immune cells and is the predominant SP signal transductor
In patients with eczema, NK1R is upregulated in monocytes, helper T cells, natural killer T cells, and basophils compared with healthy controls