[Session1. 코로나 판데믹 이후 무엇이 달라졌나?]

아토피피부염에 사용하는 새로운 약제들

나정임
서울의대 피부과

아토피피부염에 사용하는 새로운 약제들

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2024년 3월 17일 제63차 대한천식알레르기 교육강좌

Newly approved agents for AD

- PDE4 inhibitors
  - Topical crisaborole (PDE4 inhibitor, ≥age 3 months)
  - Topical difamilast (PDE4 inhibitor, ≥age 2 years in Japan, ongoing phase 3 for age 3 months ~ 2 years)
- JAK inhibitors
  - Topial ruxolitinib (JAK 1/2 inhibitor, ≥age 12 years, ≤ 20%BSA for 8weeks)
  - Topical delgocitinib (pan-JAK inhibitor, ≥age 2 years in Japan)
  - Oral baricitinib (JAK 1 inhibitor, ≥age 18 years, completed phase 3 for age 2~18 years)
  - Oral upadacitinib (JAK 1 inhibitor, ≥age 12 years, ongoing phase 1 for age 2~12 years)
  - Oral abrocitinib (JAK 1 inhibitor, ≥age 12 years)
- Biologics
  - Dupilumab (anti-IL-4Rα, ≥age 6 months)
  - Tralokinumab (anti-IL-13, ≥age 12 years in Europe, ≥age 12 years in FDA)

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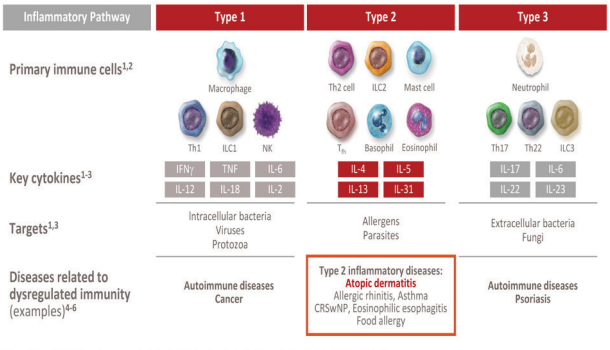
Immunologic profiles of AD



AD, atopic dermatitis; IFNγ, interferon gamma; IL, interleukin; ILC, innate lymphoid cell; NK, natural killer; Tfh, follicular helper; Th, T helper.

1. Kaiko GE, et al. *Immunology*. 2008;123:326-338. 2. Eyerich K, Eyerich S. *J Eur Acad Dermatol Venereol*. 2018;32:692-703. 3. Raphael I, et al. Cytokine. 2015;74:5-17. 4. Nakayama T, et al. *Annu Rev Immunol*. 2017;35:53-84. 5. Coates LC, et al. *Semin Arthritis Rheum*. 2016;46:291-304. 6. Gandhi NA, et al. *Expert Rev Clin Immunol*. 2017;13(5):425-437.

Immunologic profiles of AD

TABLE 1 Key characteristics of AD: Acute and chronic disease, non-lesional and lesional skin

Characteristic	Acute disease[a]	Chronic disease[b]
Type 2 pathway activation and related cytokines/chemokines	Increased (IL-4, IL-13, IL-31)[28,44,69,75,110–112]	Intensified (IL-5, IL-13, IL-31, IL-10, CCL5, CCL13, CCL18); mixed results for IL-4[28,33,44,69,75,110–112]
Type 22 pathway activation and related cytokines	Increased (IL-22)[28,44]	Intensified (IL-22, IL-32)[28,44]
Type 1 pathway activation and related cytokines/chemokines	Slightly increased (IFN-γ, MX1, IL-1β, CXCL9-11), but not in all phenotypes[32,44,51,113,114]	Significantly increased[44]
Type 17 pathway activation and related cytokines	Slightly increased (IL-17, IL-23p19, IL-23p40)[44]	Magnitude of activation is similar to that observed in acute disease[44]
Immune cell infiltration	Increased (T cells, ILC2s, DCs [mature and IDECs] and other myeloid cells)[44,115,116]	Intensified[44]
Epidermal changes	Increased hyperplasia, thickness and proliferation markers (Ki67, K16) as well as the IL-22-regulated S100A7-9 and S100A12 that mark epidermal hyperplasia;[44] reduced epidermal barrier proteins (involucrin, loricrin, filaggrin)[44]	Intensified[44]
Reduced expression of terminal differentiation proteins and lipids	Reduced expression of FLG, LOR, PPL and other differentiation proteins and significant lipid aberrations[44,61–63]	Intensified[44]

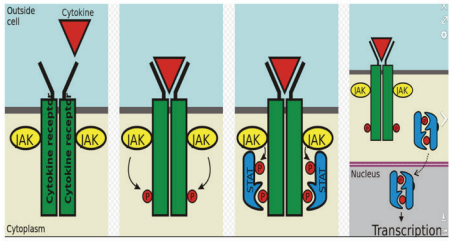
• Exp Dermatol 2019;28:756

Biologics vs Small molecule drugs

Characteristics	Biologics	Small molecule drugs
Production	Produced in cell culture	Chemically synthesized
Size	> 900 daltons	<900 daltons
Structure	Complex tertiary structure	Simple and well-defined
Stability	Unstable, sensitive to external conditions	Stable
Administration	Infusion or subcutaneous injection	Oral, topical
Half life	Long	Short

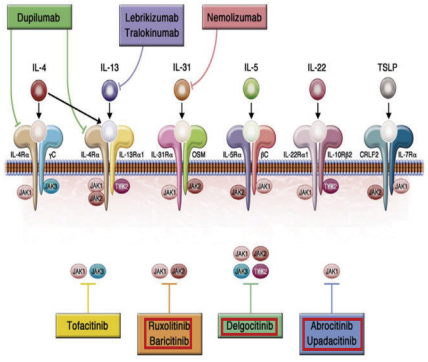
JAK-STAT Pathway

- Janus kinase
  - JAK1 , JAK2, JAK3, TYK2
- STAT (signal transducer and activator of transcription proteins)
  - STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B and STAT6



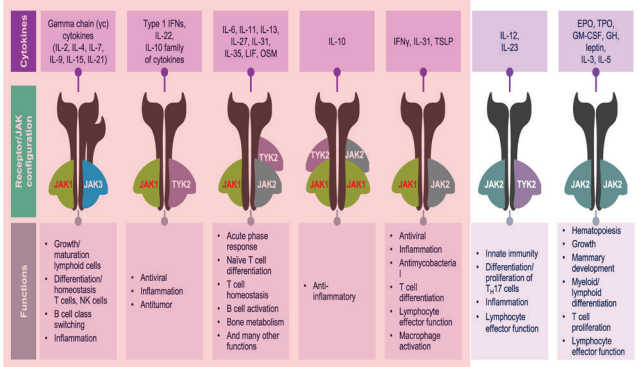
https://en.wikipedia.org/wiki/JAK-STAT_signaling_pathway#/media/File:Jakstat_pathway.svg

JAK inhibitors



J Allergy Clin Immunol 2021;148:927-40.

JAK proteins and associated cytokines

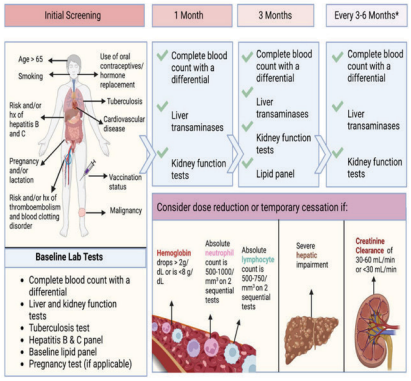


Simplified schematic highlighting different JAK-mediated signaling pathways
Abbreviations in slide notes
1. Clark JD, et al. J Med Chem 2014;57:5023–38; 2. Schwartz DM, et al. Nat Rev Drug Disc 2017;16:843–62

JAK억제제 국내 적응증 및 금기

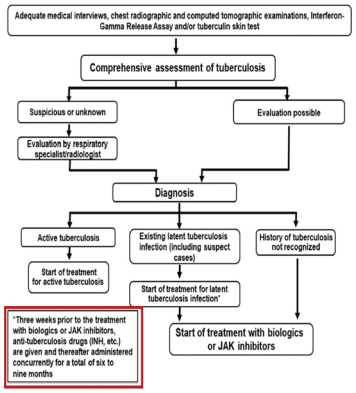
	Baricitinib (올루미언트)	Upadacitinib (린버크)	Abrocitinib (시빈코)
적응증	전신 요법 대상 성인 환자에서의 중등증 내지 중증 아토피 피부염의 치료	전신 요법 대상인 성인 및 만 12세 이상 청소년의 중등증에서 중증 아토피 피부염의 치료	전신 요법 대상인 성인 및 만 12세 이상 청소년의 중등증에서 중증 아토피 피부염의 치료
용법용량	4mg/d (75세 이상과, 만성 혹은 재발성 감염 환자는 2mg/d)	15mg/d, 필요시 30mg/d (65세 이상은 15mg/d 투여, 청소년은 체중 40kg 이상시 15mg/d, 40kg 미만은 연구가 되어 있지 않음.)	200mg/d, 증상에 따라 감량 가능 (65세 이상과 청소년은 100mg/d, 신장애시 50mg/d)
주요 부작용	Headache, herpes simplex, nasopharyngitis, CPK상승	Acne (8~15%), URI, CPK상승, neutropenia, lymphopenia, herpes simplex, herpes zoster	Nausea (8.3~17.1%), folliculitis, thrombocytopenia, nasopharyngitis, herpes simplex, herpes zoster
금기	ANC < 1000/mm3 ALC<500/mm3 , Hb <8 g/dL 는 투약 금기 (Abrocitinib은 PLT <150K/mm³ 도 투약 금기), 활동성 결핵, 중대한 감염, 임신 수유		
F/U Lab	3 개월 간격으로 CBC, LFT, Cholesterol, CPK 확인		

Screening and laboratory monitoring for patients on JAK inhibitors



Dermatol Ther (Heidelb). 2023 Mar;13(3):729-749.

Prevention of tuberculosis under treatment with JAK inhibitors



Starting biologic drugs in patients with LTBI. All guidelines recommend starting treatment with biologics 1–2 months after beginning LTBI prophylaxis (level of evidence II; strength of recommendation B). This evidence comes from the observation that initiation of anti-TNF-α therapy after 1 month of TB prophylaxis in patients with RA found positive for LTBI significantly reduced the risk of TB reactivation (level of evidence III)[7,12]. Nevertheless, if the activity of underlying disease and the global status of the patient allow, waiting 1 additional month is preferable because the side effects of the therapy with isoniazid occur mainly within the first 2 months[12].

J Dermatol. 2023 Jan;50(1):e1-e19

Pharmacokinetic profiles of JAK inhibitors

- Different PK profiles lead to different dosing requirements
- Extent of drug metabolism and distinct metabolic or biotransformative processes vary between JAK inhibitors

	Bioavailability	T_{max}	$T_{1/2}$	Elimination profile	Metabolic enzymes	Active metabolites?
Upadacitinib[1]	79%	2–4 hours	9–14 hours	Predominantly cleared via hepatic excretion	CYP3A4 (main) CYP2D6 (potential minor contribution)	No
Baricitinib[2]	79%	0.5–3 hours	~13 hours	Primarily cleared via renal excretion	CYP3A4	<10% metabolized 4 minor metabolites
Abrocitinib[3]	~60%	<1 hour	~5 hours	Primarily cleared via metabolism <1% cleared via renal excretion	CYP2C19 (~53%) CYP2C9 (~30%) CYP3A4 (~11%) CYP2B6 (~6%)	2 active metabolites

Metabolism Hepatic Renal

CYP, cytochrome P450; JAK, Janus kinase; PK, pharmacokinetic; T_{max}, time to maximum plasma concentration; $T_{1/2}$, half-life

1. RINVOQ EU Summary of Product Characteristics. Available at: https://www.ema.europa.eu/en/documents/product-information/rinvoq-epar-product-information_en.pdf (last accessed April 2022); 2. Olumiant EU Summary of Product Characteristics. Available at: https://www.ema.europa.eu/en/documents/product-information/olumiant-epar-product-information_en.pdf (last accessed April 2022); 3. Cibinqo EU Summary of Product Characteristics. Available at: https://www.ema.europa.eu/en/documents/product-information/cibinqo-epar-product-information_en.pdf (last accessed April 2022)

JAK inhibitor dose adjustment requirements in patients with hepatic or renal impairment

No dose adjustment required
Caution
Not recommended

		Upadacitinib 15 mg or 30 mg QD[1]	Baricitinib 2 mg or 4 mg QD[2]	Abrocitinib 50 mg, 100 mg or 200 mg QD[3]
Hepatic impairment	MILD	None	None	None
	MODERATE	None	None	None
	SEVERE	Contraindicated	Not recommended for use	Contraindicated
Renal impairment	MILD	None	None	No dose adjustment in patients with eGFR 60 to <90 mL/min
	MODERATE	None	2 mg QD in patients with CrCl 30–60 mL/min	Reduce dose by 50% in patients with eGFR 30 to <60 mL/min
	SEVERE	15 mg QD should be used with caution / 30 mg QD not recommended	Not recommended in patients with CrCl <30 mL/min	Recommended starting dose 50 mg QD in patients with eGFR <30 mL/min; max. daily dose 100 mg

Individual JAK inhibitors have different elimination profiles that have implications for dosing requirements in special populations

*Recommendations according to EU SmPCs. For relevant recommendations in specific regions, please refer to local labels
CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; JAK, Janus kinase; QD, once daily; SmPC, Summary of Product Characteristics

1. RINVOQ EU Summary of Product Characteristics. Available at: https://www.ema.europa.eu/en/documents/product-information/rinvoq-epar-product-information_en.pdf (last accessed April 2022); 2. Olumiant EU Summary of Product Characteristics. Available at: https://www.ema.europa.eu/en/documents/product-information/olumiant-epar-product-information_en.pdf (last accessed April 2022); 3. Cibinqo EU Summary of Product Characteristics. Available at: https://www.ema.europa.eu/en/documents/product-information/cibinqo-epar-product-information_en.pdf (last accessed April 2022)

Potential drug-drug interactions of clinical relevance

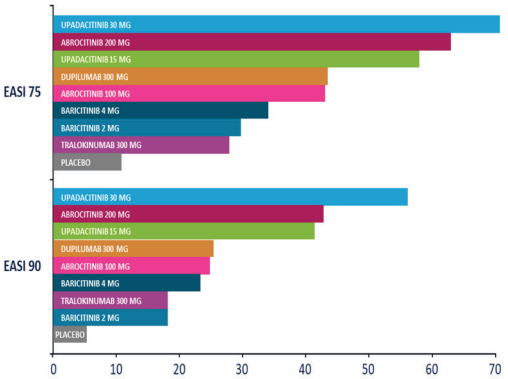
	Upadacitinib[1]	Baricitinib[2]	Abrocitinib[3]
CYP3A4 inhibitors (eg, ketoconazole, clarithromycin, ritonavir)	Use 15-mg QD dose with caution in patients receiving chronic treatment with strong CYP3A4 inhibitors / 30-mg QD dose not recommended in patients receiving chronic treatment with strong CYP3A4 inhibitors		
CYP3A4 inducers (eg, rifampicin, phenytoin)	Co-administration with strong CYP3A4 inducers (FDA)[4] / Monitor disease activity changes if co-administered with strong CYP3A4 inducers (EMA)		
CYP2C19/CYP2C9 inhibitors (eg, fluconazole)			↓ Dose by half (EMA) / Co-administration with moderate/strong CYP2C19/CYP3C9 inhibitor (FDA)[4]
CYP2C19 inhibitors (eg, fluconazole, fluoxetine, ticlopidine)			↓ Dose by half (EMA) / Use 50-mg QD (100-mg QD for patients not responding to 50-mg QD dose) in patients co-administered strong CYP2C19 inhibitors (FDA)[4]
CYP2C19/CYP2C9 inducers (eg, rifampicin, apalutamide, efavirenz, enzalutamide, phenytoin)			Co-administration with moderate/strong CYP2C19/CYP2C9 inducer
OAT3 inhibitors (eg, fluconazole, fluoxetine, ticlopidine)		↓ Dose to 1 mg QD, if taking strong OAT3 inhibitors (FDA)[4] / ↓ Dose to 2 mg QD, if taking strong OAT3 inhibitors (EMA)	
Transporters (eg, P-gp, BCRP, OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1, MATE2K)	Does not inhibit at clinically relevant concentrations[4]	Concomitant use of leflunomide or teriflunomide (EMA)	Concomitant use with dabigatran, P-gp substrates with a narrow therapeutic index, eg, digoxin (EMA) / Monitor or titrate dosage of P-gp substrate where small changes may lead to serious or life-threatening toxicities (FDA)[4]

BCRP, breast cancer resistance protein; DDI, drug-drug interaction; EMA, European Medicines Agency; FDA, Food and Drug Administration; MATE, multidrug and toxin extrusion; OAT, organic anion transporter; OATP, organic anion transporting polypeptide; OCT, organic cation transporter; P-gp, P-glycoprotein; PK, pharmacokinetic

No dose adjustment required Not recommended Caution

References in slide notes

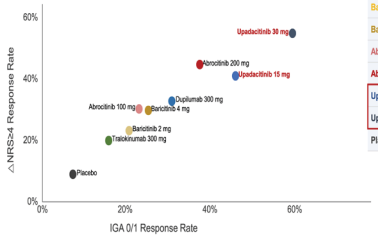
Comparison of Efficacy of Targeted Therapies without Topical Corticosteroids for Moderate to Severe Atopic Dermatitis: Systematic Review and Network Meta-analysis (2022)



Silverberg JI, et al. Dermatol Ther (Heidelb) 2022.

Comparison of Efficacy of Targeted Therapies without Topical Corticosteroids for Moderate to Severe Atopic Dermatitis: Systematic Review and Network Meta-analysis (2022)

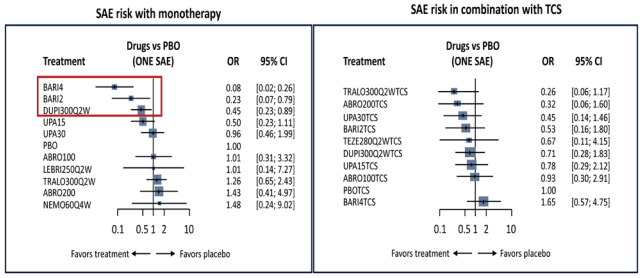
Figure 3. IGA 0/1 vs △NRS≥4 response rate estimates and 95% credible intervals at primary endpoint timepoint (Bayesian NMA fixed-effects results)



	N°	IGA 0/1	△NRS≥4
Dupilumab 300 mg	457	30.6 (16.8 – 49.0)	33.0 (16.6 – 55.0)
Tralokinumab 300 mg	1196	15.5 (7.8 – 28.5)	20.2 (9.3 – 38.6)
Baricitinib 2 mg	392	20.6 (10.2 – 37.2)	23.3 (10.5 – 44.0)
Baricitinib 4 mg	248	25.1 (12.3 – 44.3)	30.0 (14.0 – 53.2)
Abrocitinib 100 mg	314	22.9 (10.7 – 43.5)	30.6 (14.2 – 54.3)
Abrocitinib 200 mg	309	37.2 (19.3 – 60.4)	44.3 (23.0 – 68.3)
Upadacitinib 15 mg	557	46.0 (28.1 – 65.1)	42.0 (22.9 – 63.9)
Upadacitinib 30 mg	567	59.9 (40.6 – 76.5)	55.2 (33.6 – 75.1)
Placebo	2214	7.1 (3.7 – 13.1)	8.7 (4.0 – 18.0)

Silverberg JI, et al. Dermatol Ther (Heidelb) 2022.

Short-term safety of biologics and small molecule drugs: an independent systematic review and network meta-analysis



Life (Basel) 2021;11:927

Comparison of serious adverse event incidence rates btw Oral JAK inhibitors & traditional systemic treatment

Comparison of Serious Adverse Event Incidence Rates Between Oral JAK Inhibitors Approved for Atopic Dermatitis and Traditional Systemic Immunosuppressive Therapies

	Serious adverse events incidence rates (events per 100 patient-years)				
Drug	Malignancy (excluding-NMSC)	NMSC	MACE	VTE	Reference
Upadacitinib (15mg)[a]	0.2	0.4	0.1	0.1	Simpson, E.L., et al[15]
Upadacitinib (30mg)[b]	0.5	0.4	0.0	0.1	Simpson, E.L., et al[15]
Abrocitinib (100mg)[c]	0.2	0.6	0.6	0.0	Simpson, E.L., et al[16]
Abrocitinib (200mg)[d]	0.2	0.4	0.2	0.4	Simpson, E.L., et al[16]
Methotrexate	0.5	0.3	0.5	0.5	Cohen, S.B., et al[17]
Cyclosporine	0.6[f]	0.5[g]	--	DNF	Paul, C.F., et al[18]
	--	--	2.8[h]		Hong, J.R., et al[19]
Systemic Corticosteroids	4.3[i]	3.9[j]	--	--	Khan, N., et al[20]
	--	--	7.6[j]	--	Wei, L., et al[21]
	--	--	--	0.02[k]	Huerta, C., et al[22]

J Drugs Dermato. 2022;21(12):1298-1303

JAK inhibitors and cardiovascular events

Table 1 Compiled long-term safety data of Janus kinase inhibitors

	Oral Surveillance study			Six pooled studies		AD-UP 52-week extension	
	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID[a]	TNFi	Abrocitinib 100 mg daily	Abrocitinib 200 mg daily	Upadacitinib 15 mg daily	Upadacitinib 30 mg daily
Patients (total no.)	1455	1456	1451	885	1971	443	436
Average age, years	61	61	61	33	29	33	36
Person-year totals	5166	4872	10,038	500	1114	512	533
Number of adverse cardiovascular events	47	51	37	3	7	2	1
Adverse cardiovascular event/100 person-years	0.91	1.05	0.73	0.60	0.63	0.4	0.2

Elmariah SB, Smith JS, Merola JF. JAK in the [Black] Box: A Dermatology Perspective on Systemic JAK Inhibitor Safety. Am J Clin Dermatol. 2022 Jul;23(4):427-431. doi: 10.1007/s40257-022-00701-3. Epub 2022 Jun 9. PMID: 35679017

Long-term safety profile of Upadacitinib across indications: Overall safety (up to 5.5 yrs)

Exposure and overview of TEAEs

	RA			PsA		AS	AD	
Parameter	UPA 15 mg QD N=3209	ADA 40 mg EOW N=579	MTX N=314	UPA 15 mg QD N=907	ADA 40 mg EOW N=429	UPA 15 mg QD N=182	UPA 15 mg QD N=1340	UPA 30 mg QD N=1353
Exposure								
Total (PY)	9079.1	1307.7	781.7	1872.3	903.7	320.1	2035.8	2118.0
Median (minimum, maximum)[(years)]**	3.46 (0, 5.45)	2.23 (0.04, 5.44)	2.57 (0.02, 5.15)	2.25 (0, 3.9)	1.5 (0.04, 3.22)	1.76 (0.02, 3.26)	1.62 (0, 2.75)	1.65 (0, 2.84)
Overall TEAEs, E/100 PYs (95% CI)								
Any AE	205.5 (202.5, 208.5)	203.6 (196.0, 211.5)	206.9 (196.9, 217.2)	244.8 (237.8, 252.0)	229.9 (220.2, 240.0)	241.2 (224.5, 258.8)	250.5 (243.7, 257.5)	278.1 (271.0, 285.2)
Any serious AE	12.4 (11.7, 13.2)	13.7 (11.8, 15.8)	9.6 (7.5, 12.0)	11.1 (9.7, 12.7)	9.0 (7.1, 11.1)	6.6 (4.1, 10.0)	7.1 (6.0, 8.4)	8.2 (7.0, 9.5)
Any AE leading to discontinuation	4.9 (4.4, 5.3)	5.9 (4.6, 7.4)	5.8 (4.2, 7.7)	5.4 (4.4, 6.6)	5.5 (4.1, 7.3)	5.3 (3.1, 8.5)	4.5 (3.6, 5.5)	5.3 (4.4, 6.4)
Deaths,[†] E/100 PY (95% CI)	0.8 (0.6, 1.0)	0.9 (0.5, 1.6)	0.8 (0.3, 1.7)	0.8 (0.4, 1.3)	0.1 (0.0, 0.6)	0	0	0.1 (0.0, 0.4)

* 6 trials in RA, 2 trials in PsA, 1 trial in AS, 3 trials in AD
** Minimum in days are as follows: RA: UPA 15 mg, 2 days; ADA 40 mg, 14 days; MTX, 7 days. PsA: UPA 15 mg, 1 day; ADA 40 mg, 14 days. AS: UPA 15 mg, 6 days. AD: UPA 15 mg, 1 day; UPA 30 mg, 1 day.
† Non-treatment emergent deaths included.

Characterization of Acne associated with Upadacitinib

Table V. Summary of patient-reported outcomes DLQI and PGIT in responders and nonresponders according to EASI-75, EASI-90, and EASI-100 in patients with and without the adverse event of acne[a]

	DLQI		PGIT	
	Measures Up 1 and Measure Up 2 integrated data			
Mean (SD)	Acne (n = 225)	No acne (n = 1315)	Acne (n = 260)	No acne (n = 1411)
Baseline	16.9 (6.8)	16.7 (7.0)	3.2 (1.4)	3.3 (1.6)
Week 16	6.3 (6.3)	7.3 (7.2)	5.3 (1.7)	4.9 (1.9)
EASI-75				
Responders	4.3 (5.2)	3.9 (4.7)	5.8 (1.5)	5.4 (1.9)
Nonresponders	11.0 (6.1)	11.9 (7.5)	4.1 (1.5)	4.1 (1.6)
EASI-90				
Responders	3.5 (4.9)	3.0 (4.1)	5.9 (1.6)	5.6 (2.0)
Nonresponders	9.8 (6.1)	10.4 (7.5)	4.6 (1.6)	4.3 (1.7)
EASI-100				
Responders	1.7 (3.1)	1.7 (3.4)	6.0 (1.8)	5.6 (2.1)
Nonresponders	7.3 (6.4)	8.1 (7.3)	5.2 (1.6)	4.7 (1.8)

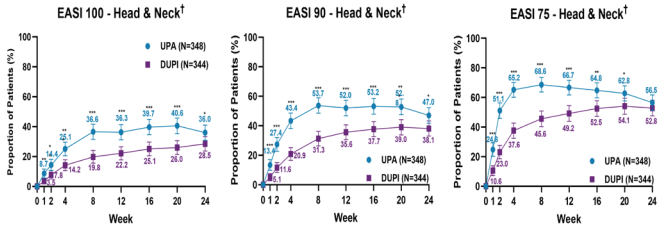
	AD Up			
	Acne (n = 115)	No acne (n = 710)	Acne (n = 126)	No acne (n = 707)
Baseline	17.5 (6.4)	16.5 (7.2)	3.7 (1.5)	3.4 (1.5)
Week 16	6.1 (5.9)	6.7 (6.6)	5.5 (1.7)	4.9 (1.9)
EASI-75				
Responders	4.6 (4.9)	4.2 (4.7)	5.8 (1.7)	5.3 (1.9)
Nonresponders	11.2 (6.2)	10.5 (7.3)	4.5 (1.5)	4.3 (1.6)
EASI-90				
Responders	3.8 (4.5)	3.3 (4.5)	5.8 (1.7)	5.4 (2.1)
Nonresponders	9.7 (5.9)	9.0 (6.8)	4.9 (1.6)	4.6 (1.7)
EASI-100				
Responders	1.6 (1.9)	1.4 (2.8)	5.4 (2.4)	5.8 (2.1)
Nonresponders	6.9 (6.0)	7.4 (6.6)	5.5 (1.6)	4.8 (1.8)

DLQI, Dermatology Life Quality Index; EASI, eczema area and severity index; PGIT, Patient Global Impression of Treatment; SD, standard deviation.
[a]Populations stratified by the baseline presence of acne.
[b]DLQI was administered only in patients 16 years of age or older.

- Acne was clinically manageable, and almost half the patients required no intervention; most patients who required intervention only used topical therapies. Systemic therapies were used infrequently, as 4.8% and 7.6% of patients who developed acne while taking upadacitinib 15 mg and 30 mg, respectively, required oral treatment, mainly tetracycline antibiotics;
- The occurrence of acne had no effect on patient QoL. In addition, acne also had no impact on patient satisfaction with upadacitinib as measured using the PGIT.

Upadacitinib vs Dupilumab Efficacy for Head and Neck

Proportions of patients achieving:

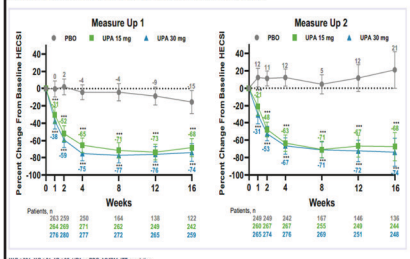


*:p≤0.05, **:p≤0.01, ***:≤0.001; unranked endpoints are not multiplicity controlled, all p-values are nominal
†EASI 75/90/100 - Head & Neck defined as at least a 75/90/100 percent reduction in Eczema Area and Severity Index subscore in the Head and Neck region
ITT population; NRI-C, Non-Responder Imputation incorporating Multiple Imputation [MI] to handle missing data due to COVID-19; EASI, Eczema Area and Severity Index; DUPI, dupilumab; UPA, upadacitinib

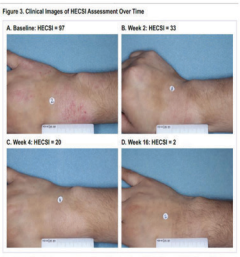
UPA vs DUPI for AD in Four Body Regions

Effect of Upadacitinib on Hand Eczema in Patients With Moderate-to-Severe AD : Results From Two Phase 3 Trials (Measure Up 1 and Measure Up 2)

Figure 2. LS Mean Percent Change in Baseline HECSI (MMRM)

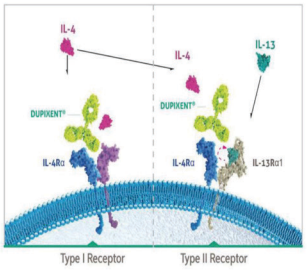


***P≤0.001, **P≤0.01, *P≤0.05, UPA vs PBO; MMRM, ITT population.
HECSI, Hand Eczema Severity Index; ITT, intent-to-treat; MMRM, Mixed-Effect Model Repeat; PBO, placebo; UPA, upadacitinib.



Dupilumab - Mechanism of action

- A fully human monoclonal antibody targeting the IL-4Rα
  - Blocks IL-4/IL-13-driven type 2 inflammation.



J Am Acad Dermatol 2019;81:143.

Dupilumab 아토피피부염 국내 적응증과 급여 기준 (2024년 2월 현재)

허가사항 (적응증)
- (만 6개월 이상)국소치료제로 적절히 조절되지 않거나 이들 치료제가 권장되지 않는 중등도에서 중증 아토피피부염

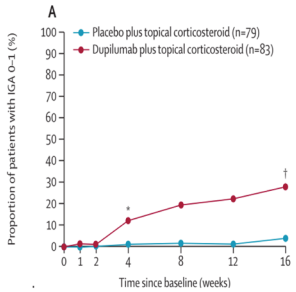
급여기준
- 3년 이상 증상이 지속되는 EASI 23점 이상의 만성 중증 성인 및 만12-17세 청소년 아토피피부염 환자로 국소치료제, 전신치료제를 투여하였음에도 적절히 치료되지 않은 경우
- 1년 이상 증상이 지속되며, 1차 국소치료제를 4주 이상 투여하였음에도 적절히 조절되지 않은 EASI 21점 이상의 만 6~11세 아토피피부염 환자 (소아의 경우 사진 반드시 제출)

항목	허가사항 (적응증)	성인과 청소년 급여기준	소아 급여기준
나이	만6개월 이상	만12세 이상	만6세 이상
중증도	중등도에서 중증 아토피피부염	EASI 23점 이상의 중증 아토피피부염	EASI 21점 이상의 중증 아토피피부염
치료력 (국소치료제)	국소치료제로 적절히 조절되지 않거나 이들 치료제가 권장되지 않는	중등도 이상의 TCS 혹은 TCI 4주 이상 사용하였음에도 적절히 조절되지 않음*	중등도 이상의 TCS 혹은 TCI 4주 이상 사용하였음에도 적절히 조절되지 않음*
치료력 (전신치료제)	해당 사항 없음	전신 면역억제제 (Cyclosporin 혹은 MTX)를 3개월 이상 투여하였음에도 반응이 없거나 (EASI-50 미달성 등)이 없거나 부작용 등으로 사용할 수 없는 경우*	해당 사항 없음

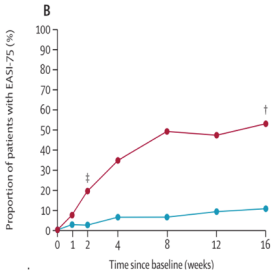
* 듀피젠트 투약개시일 6개월 이내에 국소치료제 및 전신 면역억제제 투여이력이 확인되어야 함

Dupilumab in children aged 6 Mo - 5 Yrs: Efficacy

IGA 0/1 28% vs 4%



EASI-75 53% vs 11%



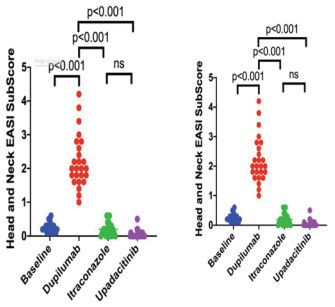
Lancet 2022 Sep 17;400(10356):908-919.

Dupilumab in children aged 6 Mo - 5 Yrs: Safety

	Dupilumab plus topical corticosteroid (n=83)	Placebo plus topical corticosteroid (n=78)*
Overview		
Patients with ≥1 treatment-emergent adverse event	53 (64%)	58 (74%)
Patients with treatment-emergent adverse events leading to treatment discontinuation	1 (1%)†	1 (1%)‡
Patients with ≥1 serious treatment-emergent adverse event	0	4 (5%)§
Deaths	0	0
Patients with ≥1 severe treatment-emergent adverse event	2 (2%)	10 (13%)
Patients with ≥1 treatment-emergent adverse event deemed related to study drug	9 (11%)	5 (6%)
Patients with treatment-emergent adverse event of special interest	1 (1%)¶	0
Narrow conjunctivitis‖	4 (5%)	0
Allergic conjunctivitis	1 (1%)	0
Conjunctivitis	3 (4%)	0
Skin infections excluding herpes viral infections**	10 (12%)	19 (24%)
Herpes viral infections††	5 (6%)	4 (5%)
Injection-site reactions††	2 (2%)	2 (3%)

Lancet 2022 Sep 17;400(10356):908-919.

Dupilumab-associated head and neck dermatitis resolves temporarily with itraconazole therapy and rapidly with transition to upadacitinib, with *Malassezia*-specific immunoglobulin E levels mirroring clinical response



J Am Acad Dermatol. 2023 Jan;88(1):255-257.

Dupilumab and conjunctivitis risk factors

- Older AD patients with more advance disease
- Longer period of AD
- Have other atopic comorbidities
- Prior history of allergic conjunctivitis

Dupilumab and conjunctivitis

- Dupilumab 투여 중 발생한 Ocular Surface Disease in Adults (캐나다 연구)
  - 210명의 dupilumab 투여 환자 중 37% (n=78)에서 Dupilumab-induced ocular surface disease (DIOSD)발생
    - Corneal scarring and cicatricial ectropion 1% (n=3)
    - Blepharoconjunctivitis 68%
    - Burning/stinging/dryness 14%
    - Epiphora 13%
    - Pruritus 13%
    - Blurred vision 3%
    - Photophobia 1%

Cornea 2022;41 (10): 1242-1247.

Dupilumab and cicatricial ectropion

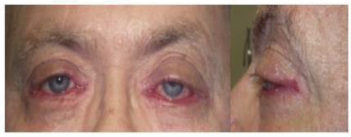


Fig. 1. External photos showing bilateral conjunctival hyperemia, upper eyelid edema, and cicatricial ectropion (left greater than right). Additionally, there is left-sided blepharoptosis.

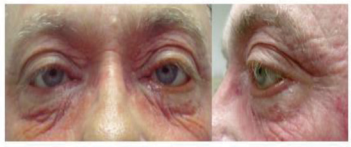


Fig. 2. External photos showing bilateral resolution of conjunctivitis, eczematous reaction of lower eyelids and cheeks, and persistent cicatricial ectropion (left greater than right) following discontinuation of dupilumab and prednisone taper.

Am J Ophthalmol Case Rep. 2017 Jun 22;7:120-122

Dupilumab 그 밖의 적응증

- 만 18세 이상 성인에서 국소치료제로 적절히 조절되지 않거나 이들 치료제가 권장되지 않는 중등도에서 중증 결절성 양진 (2023년 12월)
- 1세 이상 호산구성 식도염 (FDA 2024년 1월)
- 6세 이상 기존 치료로 호전되지 않는 중등도에서 중증 천식
- 18세 이상 비용종을 동반한 중증 만성비부비동염

Dupilumab, 결절성 양진 3상 임상시험 결과

nature medicine

Dupilumab in patients with prurigo nodularis: two randomized, double-blind, placebo-controlled phase 3 trials

Prurigo nodularis (PN) is a chronic inflammatory skin disease with intensely pruritic nodules. The LIBERTY-PN PRIME and PRIME2 phase 3 trials enrolled adults with PN with ≥20 nodules and severe itch uncontrolled with topical therapies. Dupilumab, a fully human monoclonal antibody, blocks the shared receptor component for interleukin (IL)-4 and IL-13. Patients were randomized 1:1 to 300 mg dupilumab or placebo subcutaneously every 2 weeks for 24 weeks. The primary endpoint was pruritus improvement, measured by proportion of patients with a ≥4-point reduction in Worst Itch Numeric Rating Scale (WI-NRS) from baseline at week 24 (PRIME) or week 12 (PRIME2). Key secondary endpoints included nodule number reduction to ≤5 at week 24. PRIME and PRIME2 enrolled 151 and 160 patients, respectively. Both trials met all the pre-specified primary and key secondary endpoints. A ≥4-point WI-NRS reduction at week 24 in the dupilumab and placebo arms was achieved by 60.0% and 18.4% of patients, respectively, in PRIME (95% confidence interval (CI), 27.8–57.7 for the difference, $P < 0.001$) and at week 12 by 37.2% and 22.0% of patients, respectively, in PRIME2 (95% CI, 2.3–31.2; $P = 0.022$). Dupilumab demonstrated clinically meaningful and statistically significant improvements in itch and skin lesions versus placebo in PN. Safety was consistent with the known dupilumab safety profile.

Nature Medicine | Volume 29 | May 2023 | 1180–1190

Dupilumab, 결절성 양진 3상 임상시험 결과

Table 2 | Efficacy outcomes

Efficacy endpoints	PRIME				PRIME2			
	Placebo *n*=76	Dupilumab 300 mg every 2 weeks *n*=75	Difference versus placebo, % (95% CI)	*P* value versus placebo (place in the testing hierarchy)	Placebo *n*=82	Dupilumab 300 mg every 2 weeks *n*=78	Difference versus placebo, % (95% CI)	*P* value versus placebo (place in the testing hierarchy)
Primary and key secondary outcomes								
WI-NRS improvement (reduction) by ≥4 from baseline to week 24[a], *n* (%)	14 (18.4)	45 (60.0)	42.7 (27.8 to 57.7)	<0.001 (1)	16 (19.5)	45 (57.7)	42.6 (29.1 to 56.1)	<0.001 (2)
WI-NRS improvement (reduction) by ≥4 from baseline to week 12[b], *n* (%)	12 (15.8)	33 (44.0)	29.2 (14.5 to 43.8)	<0.001 (not multiplicity-controlled)	18 (22.0)	29 (37.2)	16.8 (2.3 to 31.2)	0.022 (1)
IGA PN-S score of 0 or 1 ('clear' or 'almost clear') at week 24[a], *n* (%)	14 (18.4)	36 (48.0)	28.3 (13.4 to 43.2)	<0.001 (2)	13 (15.9)	35 (44.9)	30.8 (16.4 to 45.2)	<0.001 (3)
Concomitant WI-NRS improvement (reduction) by ≥4 points from baseline and IGA PN-S score of 0 or 1 at week 24[a], *n* (%)	7 (9.2)	29 (38.7)	29.6 (16.4 to 42.8)	<0.001 (3)	7 (8.5)	25 (32.1)	25.5 (13.1 to 37.9)	<0.001 (4)

Nature Medicine | Volume 29 | May 2023 | 1180–1190