아토피피부염의 전신치료에 대한 업데이트

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2024
한국 아토피피부염 치료 가이드라인

중등증/중증 아토피피부염
약물치료 최신 업데이트

	Mild AD	Moderate to severe AD
Basic therapies	▪ **Moisturizer,** avoidance of allergens, **educational program** (**multidisciplinary team approach** and structured educational materials)	
Topical therapies	▪ **Topical corticosteroids (acute and proactive)** ▪ **Topical calcineurin inhibitors (reactive and proactive)** ▪ Wet wrap therapy (acute)	
Systemic therapies		▪ **Conventional systemic drugs: cyclosporine,** methotrexate, azathioprine, corticosteroids (short-term) ▪ **Biologics: dupilumab tralokinumab lebrikizumab** nemolizumab ↕* ↔* ▪ **JAK inhibitors: baricitinib upadacitinib abrocitinib** ↕*
Other therapies	▪ **Antibiotics (infected state)** ▪ Antihistamines ▪ Antifungals (head and neck dermatitis)	▪ Phototherapy ▪ Allergen-specific immunotherapy

The text in bold indicates a treatment with strength of recommendation A (strong recommendation for using an intervention).
*Switchable in insufficient response† or intolerable due to adverse effects
†Insufficient response: as AD who failed to reach to EASI 50, or meets one or more of the following criteria after 3 months appropriate treatment: day time or nighttime itch with itch numeric rating scale (NRS) score ≥4, or dermatology life quality index (DLQI) ≥6

Content

- Indication of systemic treatment
- Biologics and JAK inhibitors
  - ✓ MOA
  - ✓ Effect
  - ✓ Adverse events
  - ✓ Monitoring
- Unveiling future therapeutic directions

When to Consider Systemic Therapy

Scale Definition

- ✓ > EASI 15
- ✓ SCORAD above 50

Functional Definition

- ✓ Fail of response to topical therapy
- ✓ if excessive amounts of topical corticosteroids (TCSs) are needed to control persistent or frequently recurring AD
- ✓ intolerant, or unable to use medium- or higher-potency topical therapies

Social Definition

- ✓ Severe impairment of QOL

- Peak Pruritus NRS >7
- Face, Hand & Foot, Genital…

<Shared Decision-Making, SDM>
Collaboratively between clinicians and the patients or caregivers

Severity spectrum of atopic dermatitis

Systemic treatment

Mild	Moderate	Severe	Most Severe
EASI 1-7	EASI 7-20 ≥6 7.1-21.0 ≥16	EASI >21	
SCORAD <25	SCORAD 25-50	SCORAD >50	
IGA 1-2	IGA 3	IGA 4	
	BSA <10	BSA 10-30	BSA ≥30
Korea (2019), Reimbursement criteria			
EASI <6	EASI 6-22.9	EASI ≥23	

Original Article | Annals of Dermatology 2021;33(6):497-514 • https://doi.org/10.5021/ad.2021.33.6.497

Check for updates

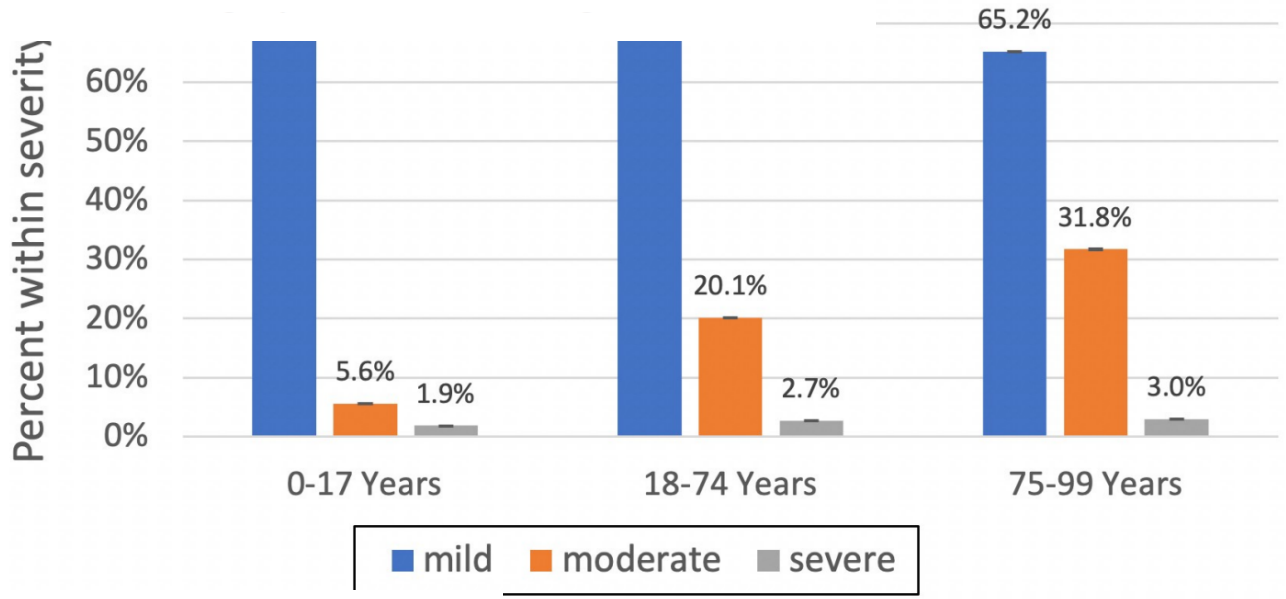
Consensus Update for Systemic Treatment of Atopic Dermatitis

Ji Hyun
Seung P
Young-J

Moderate to severe AD: objective EASI≥16*

10% of patients with AD received systemic therapy

→ up to one-third of children with AD



Mean percentage of patients in each age group (children, adults, and older , and severe atopic dermatitis. Bars indicate 95% confidence intervals.

Characteristics	Pediatrics (n=944,559)	Adults (n=1,066,453)
Moderate-to-severe AD*, n (%)	14,268 (1.5)	44,298 (4.2)

PLoS One. 2021;16:e0258219

Indications

- **Japanese** guidance (2023)
  - EASI score: ≥16
  - body surface area: ≥10%
  - or extensive eruption of the face
    - as a reference, EASI score of the **head and neck: ≥2.4**

- **Portuguese** recommendations (2021)
  - with an EASI score <16 but at least one of the following conditions:
    - Localization on the **face, hands or genitals**...
    - **Pruritus** with numeric rating scale (NRS) score >7
    - **Sleep disturbances** with NRS score >7
    - Significant negative impact on physical, psychological or social functioning (DLQI >10)

Indication for systemic treatment

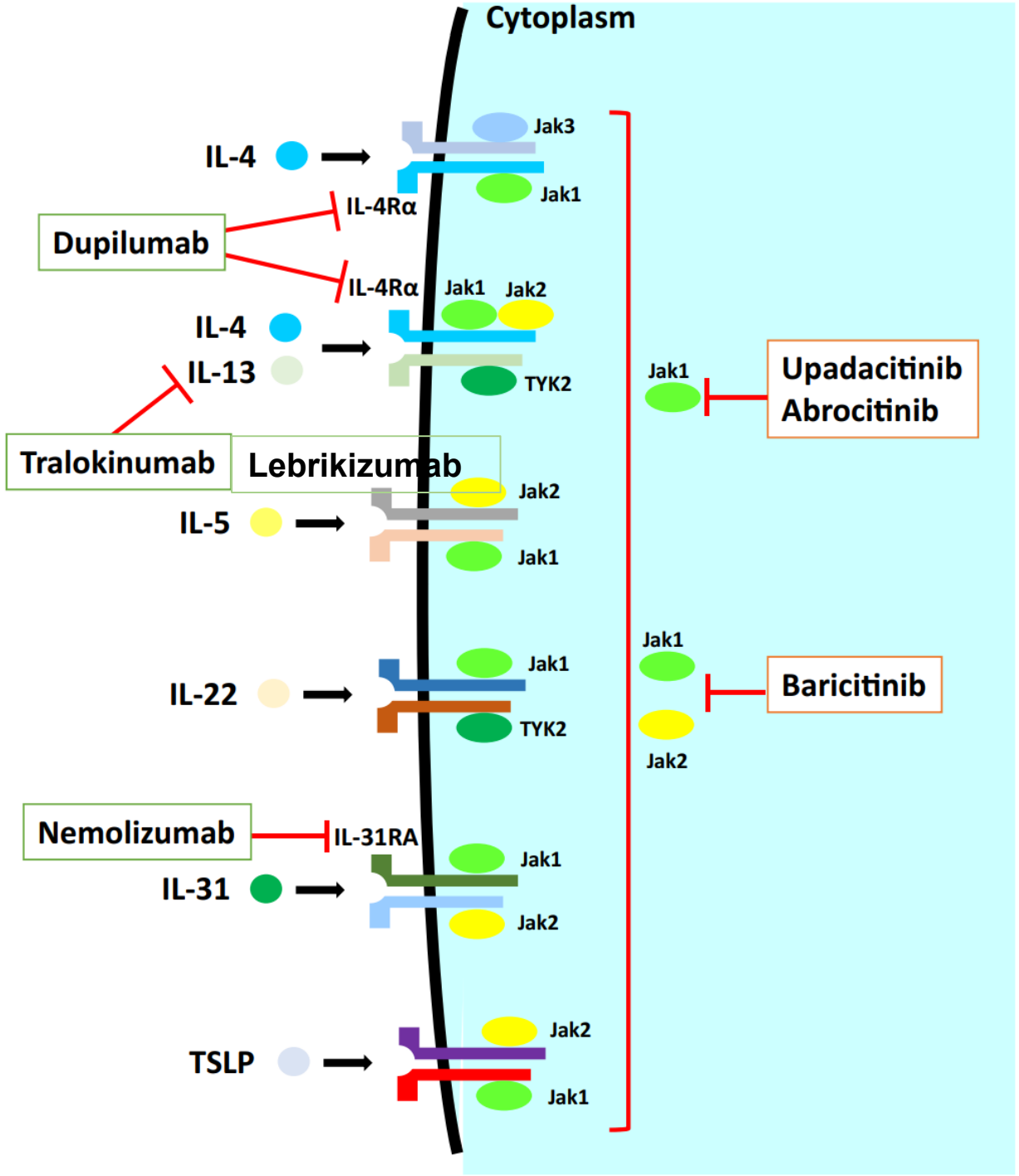
Traditional systemic immunosuppressive agents

- Short-term treatment
- Flare
- Severe

- such as cyclosporine, azathioprine and methotrexate, has been shown to be effective in patients failing topical treatment and, until late 2017, were the only agents available to treat severe, refractory AD

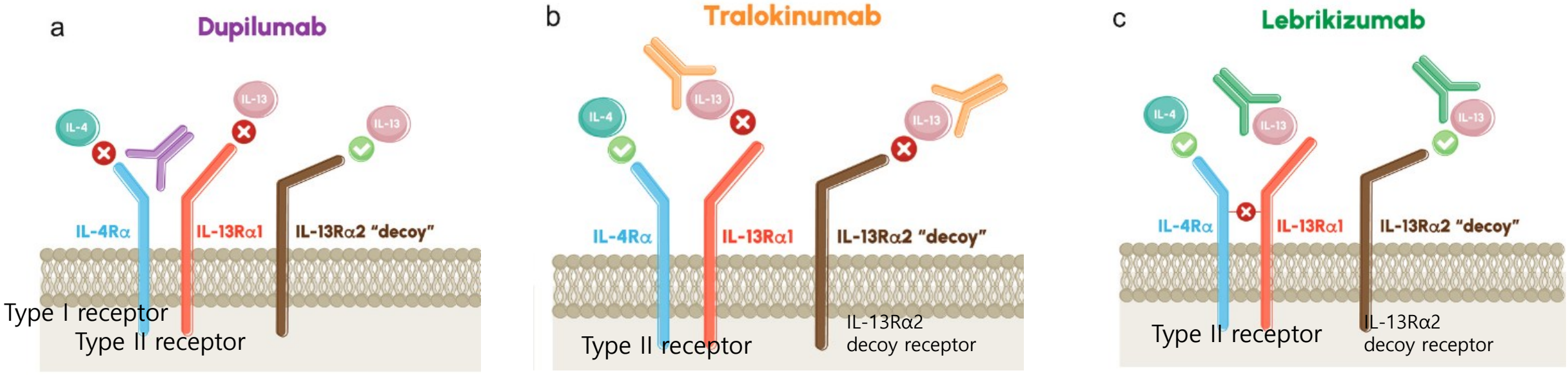
Advanced therapy

- Long-term
- Moderate to severe

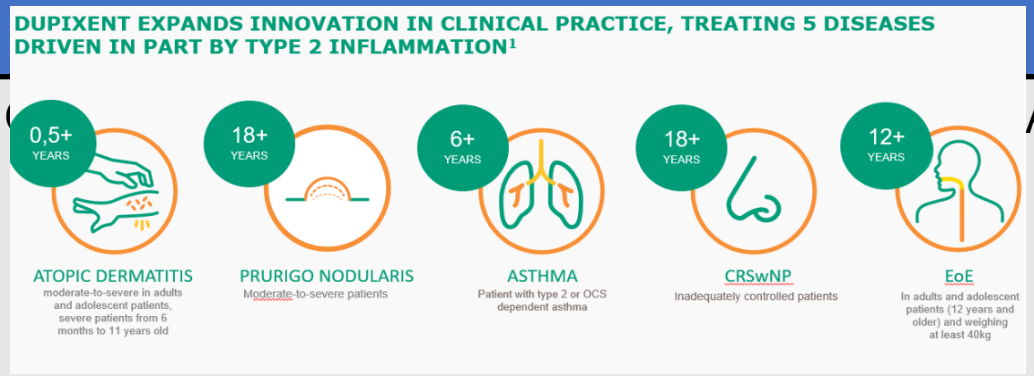


- ✓ MOA
- ✓ Effect
- ✓ Adverse events
- ✓ Monitoring

	Dupilumab	Tralokinumab	Lebrikizumab
FDA Approval	2017, DUPIXENT® Sanofi	2021, Adtralza® (tralokinumab) / Adbry® (tralokinumab-ldrm) / LEO	2024, Ebglyss® Lilly
MoA	Receptor blocker	Cytokine inhibitor	Cytokine inhibitor
	IL-4 receptor alpha antagonist		
	Dual blockade of IL-4 and IL-13 signaling (type I, II receptor)	IL-13 type II receptor	IL-13 type II receptor
IL-13Rα2 decoy receptor	-	Inhibition (lysosomal mediated clearance of IL-13 from the cell)	-



	Dupilumab	Tralokinumab	Lebrikizumab
MoA	Receptor blocker	Cytokine inhibitor	Cytokine inhibitor
Affinity	12 pM	58-904 pM	6.3 pM
Bioavailability	61-64%	60-76%	86%
Half time	Unknown in humans, 4.8-20.5 days in animal models	22days	24.5 days
	Human immunoglobulin G4 monoclonal antibody	Human immunoglobulin G4 monoclonal antibody	Humanized IgG4 antibody
ADA	6% (neutralizing Ab 1%)	4.6% (1%)	Neutralizing Ab: 2.8%

	Dupilumab	Tralokinumab	Lebrikizumab
INDI		AD	AD
DOSAGE AND ADMINISTRATION	≥ 6 months of age Pen formulation is currently being tested in 6 to 11-year-olds 600 mg (two 300 mg injections) → 300 mg Q2W	≥12 years Initial dose of 600 mg (four 150 mg injections) → 300 mg (two 150 mg injections) at every other week. • **After 16 weeks** of treatment, for patients with body weight below 100 kg who achieve clear or almost clear skin, a dosage of **300 mg every 4 weeks** may be considered.	≥12 years 500 mg (two 250 mg injections) at Week 0 and Week 2 → 250 mg every 2 weeks until Week 16 or later • After Week 16 when adequate clinical response is achieved Maintenance dose : **250 mg every 4 weeks**

ADULTS (18+ years)

	Day 1	Dosing frequency	Subsequent doses
	300 mg + 300 mg	Q2W	300 mg

ADOLESCENTS (12–17 years)

	Day 1	Dosing frequency	Subsequent doses
≥60 kg	300 mg + 300 mg	Q2W	300 mg
<60 kg	200 mg + 200 mg	Q2W	200 mg

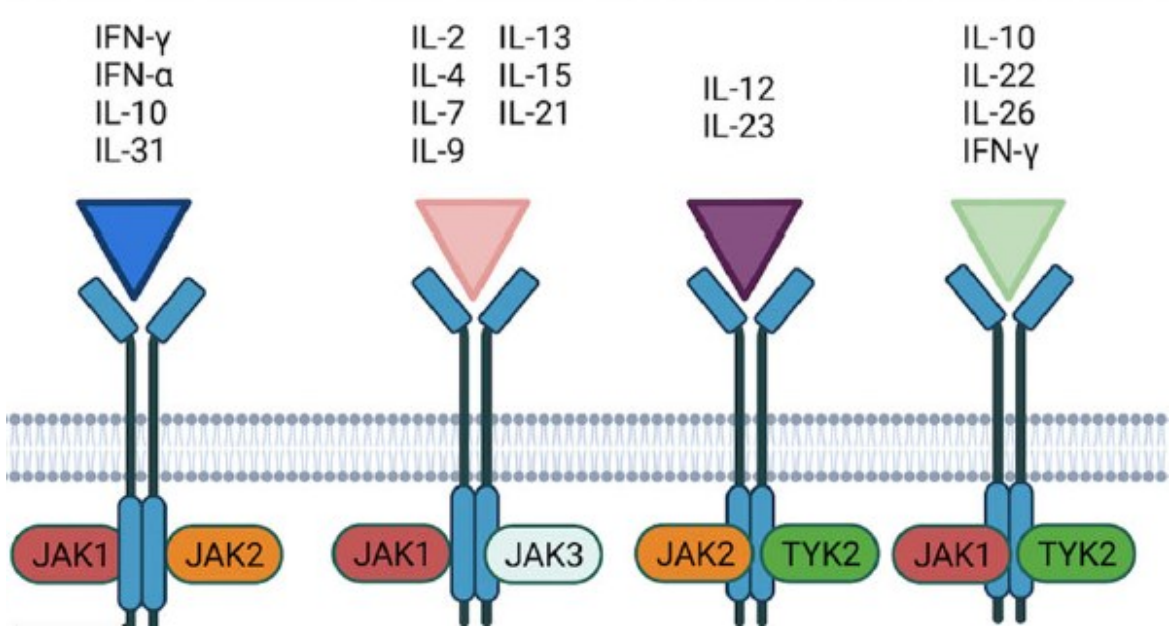
CHILDREN (6–11 years)

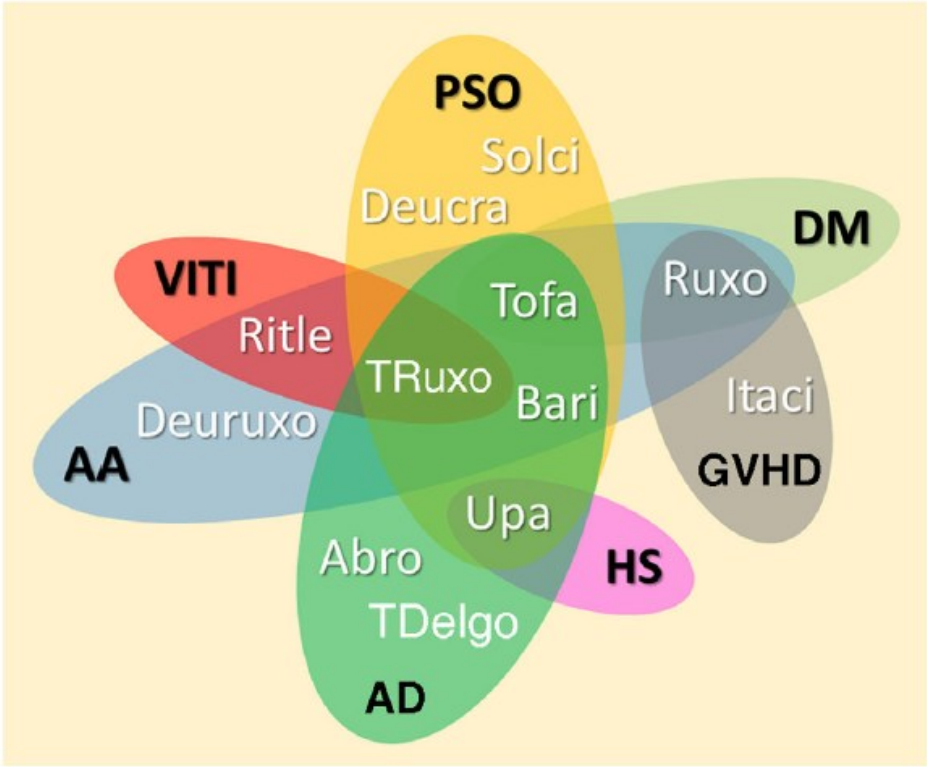
	Day 1	Dosing frequency	Subsequent doses
≥60 kg	300 mg + 300 mg	Q2W	300 mg
15 kg to <60 kg	300 mg (Day 1), 300 mg (Day 15)	Q4W† starting 4 weeks after Day 15 dose	300 mg

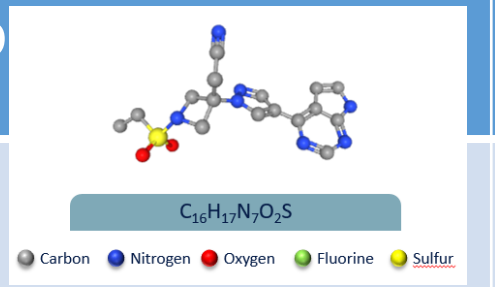
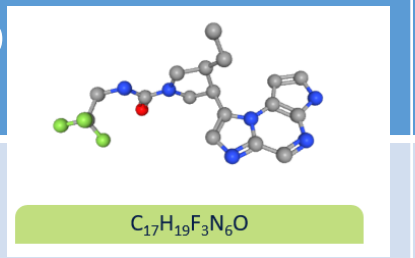
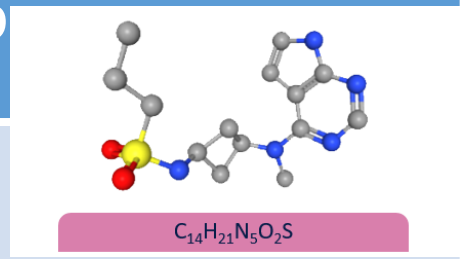
INFANTS (6 months–5 years)

	Day 1	Dosing frequency	Subsequent doses
15 kg to <30 kg	300 mg	Q4W	300 mg
5 kg to <15 kg	200 mg	Q4W	200 mg

Baricitinib	Upadacitinib	Abrocitinib
Lilly	AbbVie	Pfizer
JAK 1/JAK 2 inhibitor	Selective JAK 1 inhibitor	Selective JAK 1 inhibitor
1,2,4 mg	15 and 30 mg, 45mg	50, 100 and 200 mg
2020년	2021년	2022년
≥2 years of age	≥12 years	≥12 years





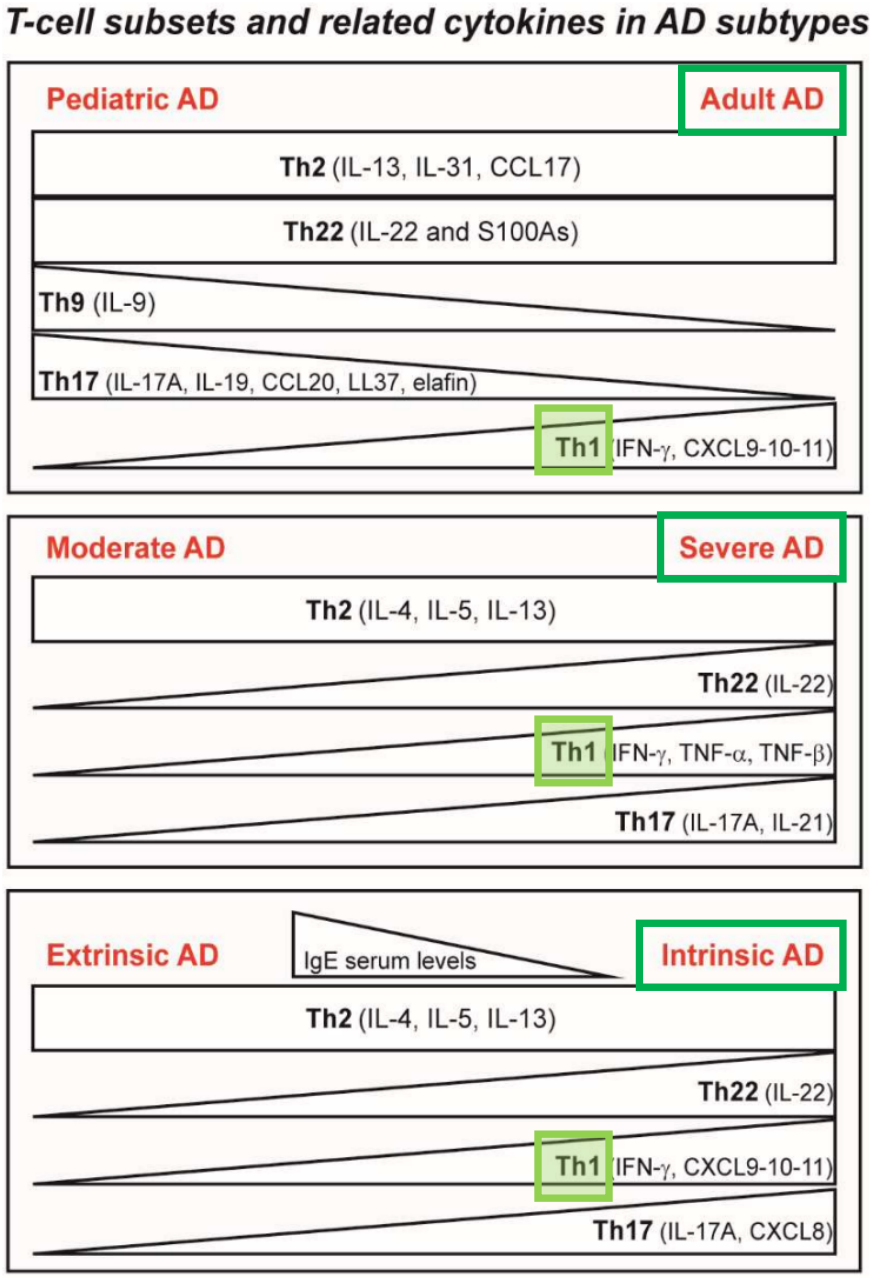
Baricitinib	Upadacitinib	Abrocitinib
		
AD, AA, RA, JIA	AD, PsoA, RA, axSpA, UC, CD	AD
1,2,4 mg	15 and 30 mg, 45mg	50, 100 and 200 mg
≥2 years of age	≥12 years	≥12 years
체중 10kg 이상 30kg 미만: 1일 1회 2mg 경구 투여 **체중 30kg 이상:** 1일 1회 4mg 경구 투여	체중 ≥ 40kg, 1일 1회 15mg • 적절한 반응이 나타나지 않는 경우, 65세 미만의 성인과 청소년에서는 1일 1회 30mg으로 증량	**성인 및 12세 이상 청소년 (체중 ≥ 40kg):** 1일 1회 100mg • 반응이 충분하지 않은 경우, 1일 1회 200mg으로 증량
Adult half life : ~12 to 16 hours	~ 8 to 14 hours	~3 to 5 hours

Central role

Th2 Target therapy

→ Biologics

Near complete inhibition of a single cytokine



Broad

→ JAKi

Partially and reversibly modulate the signaling of multiple pathways

Int. J. Mol. Sci. 2022;23:2684

Characteristics of JAK Inhibitors

1. Selectivity, but is relative
   - Selective JAK1 inhibitor
     - Abrocitinib : JAK1 > JAK2 > TYK2 > JAK3
     - Upadacitinib : JAK1 > JAK2 > JAK3 > TYK2
   - Selective JAK1/2 inhibitor
     - Baricitinib : JAK1 = JAK2 > TYK2> JAK3

Effectiveness
→ Dosing

2. Pharmacokinetics/Pharmacodynamic characteristic
   - Half-life / Primary metabolizing enzymes / Primary clearance mechanism / Birth control
     - Abrocitinib : 2.8–5.4h / CYP2C19 and CYP2C9 / Urine / 4 weeks
     - Upadacitinib : 8-14h / CYP3A4 / Urine, feces / 4 weeks
     - Baricitinib : 12-16h /CYP3A4 / Urine / 1 week

3. Off-target inhibition of non-JAKs

Acta Dermatovenerol Croat. 2023;31:162-164

Characteristics of JAK Inhibitors

1. Selectivity

2. Pharmacokinetics/Pharmacodynamic characteristic

3. Off-target inhibition of non-JAKs
   - binding to kinases other than JAKs
     - due to the highly conserved structure of the catalytic sites of protein kinases
       - Abrocitinib : inhibited VEGF receptor 2
       - Baricitinib : high binding affinity for adaptor associated protein kinase 1 and cyclin G-associated kinase (viral endocytosis)
       - Upadacitinib : inhibition of Rho-associated kinases (Rock)1 and 2 (cardiac fibrosis and hypertrophy)

         → clinical relevance ?

Rheumatology. 2024;63:298–308

Some practical issues pertaining to oral JAK inhibitors, see each monograph[29-31] for more details:

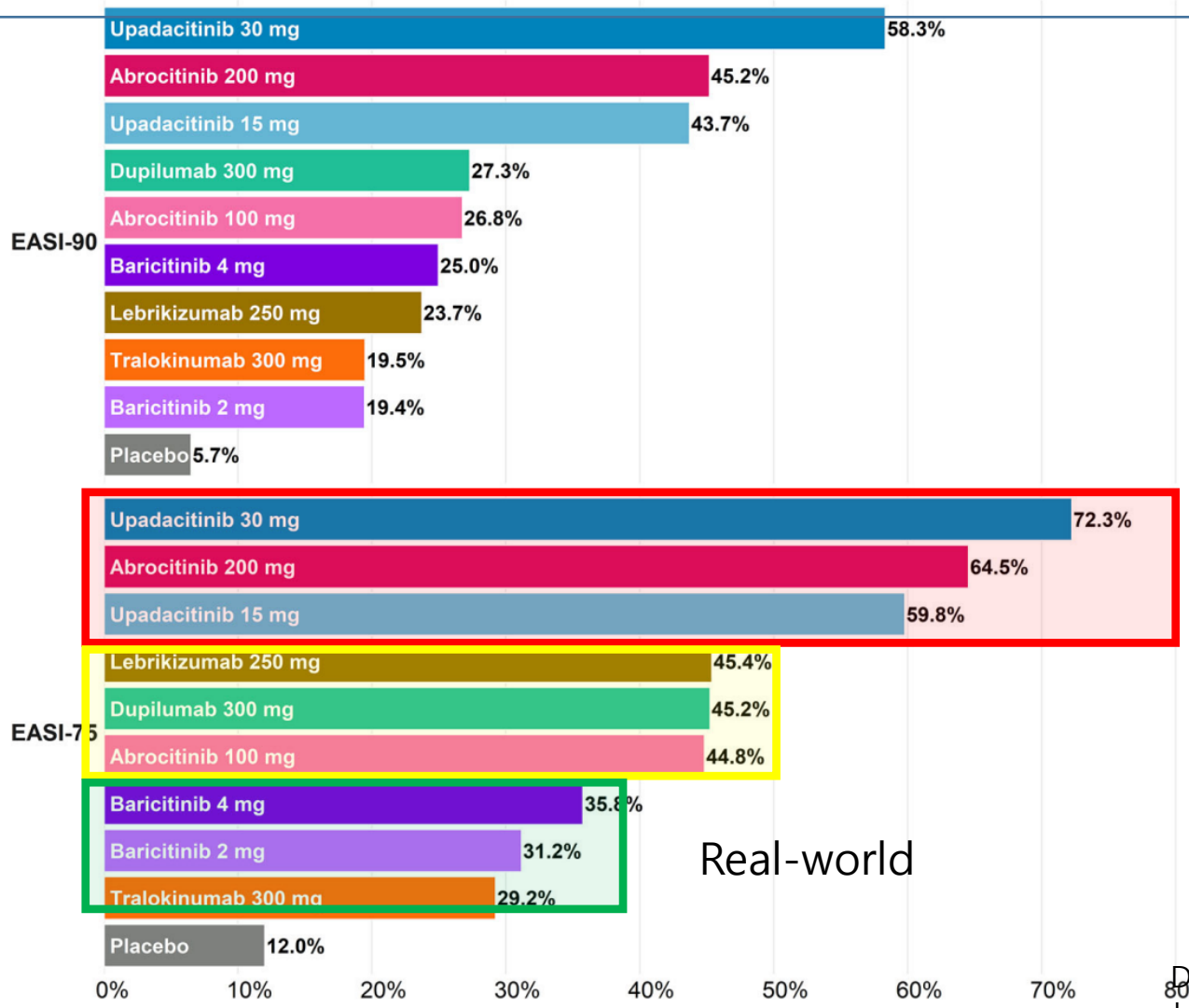
Drug (alphabetical order)	Abrocitinib	Baricitinib	Upadacitinib
Brand name	Cibinqo	Olumiant	Rinvoq
AD Drug marketing approval	FDA, HC, EMA	EMA (Not FDA or HC)	FDA, HC, EMA
Boxed warning?	Yes	Yes	Yes
Age indication	≥12 years	≥18 years (EMA, MHRA)	≥12 years and ≥40 kg
Drug interactions	Extensive, use of formal drug-interaction assessment advised		
Drug metabolism (All 3 metabolized by liver)	Lower dose in **CYP2C19 poor metabolizers. Substrate** of CYP2B6 (minor), **CYP2C19 (major), CYP2C9 (major),** CYP3A4 (minor), OAT1/3; **Inhibits** P-gp/ABCB1	**Substrate** of BCRP/ABCG2, **CYP3A4** (minor), **OAT1/3**, P-glycoprotein/ABCB1 (minor);	**Substrate** of CYP2D6 (minor), **CYP3A4 (major); Induces** BCRP/ABCG2, CYP3A4 (weak), OATP1B1/1B3 (SLCO1B1/1B3)
Other food/drug interactions	Antiplatelet agents (e.g. aspirin) in first 3 months.	-	Grapefruit, macrolides (CYP3A4; up to a week).
Adult half-life	~3 to 5 hours	~12 to 16 hours	~8 to 14 hours
Doses (tablets) available	50, 100, or 200 mg	1, 2 or 4 mg	15, 30, or 45 mg
Wholesale price per pill	~$200 USD	~$100 to $200 USD	~$245 to $490 USD
Doses with best evidence	100 or 200 mg	2 or 4 mg	15 or 30 mg
Doses per day	1	1	1
Adjust dosing if	Renal impairment. Do not use in severe renal or liver disease. If infections, low blood count, or other complications, hold drug until issue cleared.		

Summary of AD Yardstick[32] and monographs[29-31]. Some experts avoid CYP3A4 inhibitors with any JAKib.

1M	BARI 2mg	BARI 4mg	ABRO 50mg	ABRO 100mg	ABRO 200mg	UPA 15mg	UPA 30mg
급여	13,448	20,172	11087	17,739	25,942	18,740	29,850
30일 처방	403,440	605,160	332,610	532,170	778,260	562,200	895,500
산특	40,344	60,516	33,261	53,217	77,826	56,220	89,550
본인부담	17,490	26,230	14,420	23,070	33,730	24,370	38,810
30일 약제비	524,700	786,900	432,600	692,100	1,011,900	731,100	1,164,300

Efficacy of Advanced treatment

- ✓ Week 12 for abrocitinib, week 16 for all other therapies
- ✓ Without topical steroid



Real-world

Optimal target

EASI-90
27-58%

Moderate target

EASI-75
45-72%

Dermatol Ther 2023;13:2247–2264
J Eur Acad Dermatol Venereol. 2024;38:2139-2148

scientific reports 2024;14:16934

Check for updates

OPEN

Drug survival analysis of dupilumab and associated predictors in patients with atopic dermatitis in South Korea: single-cente retrospective study

Tae Woong Seul, Hyun Woo Park, Hyo Yoon Kim, Jung Jin Shin & Sang Wo

1. Injection-site erythema and/or pain
2. Ocular adverse events
3. Facial erythema
4. Psoriasiform dermatitis
5. Joint pain/inflammatory arthritis
6. Alopecia areata

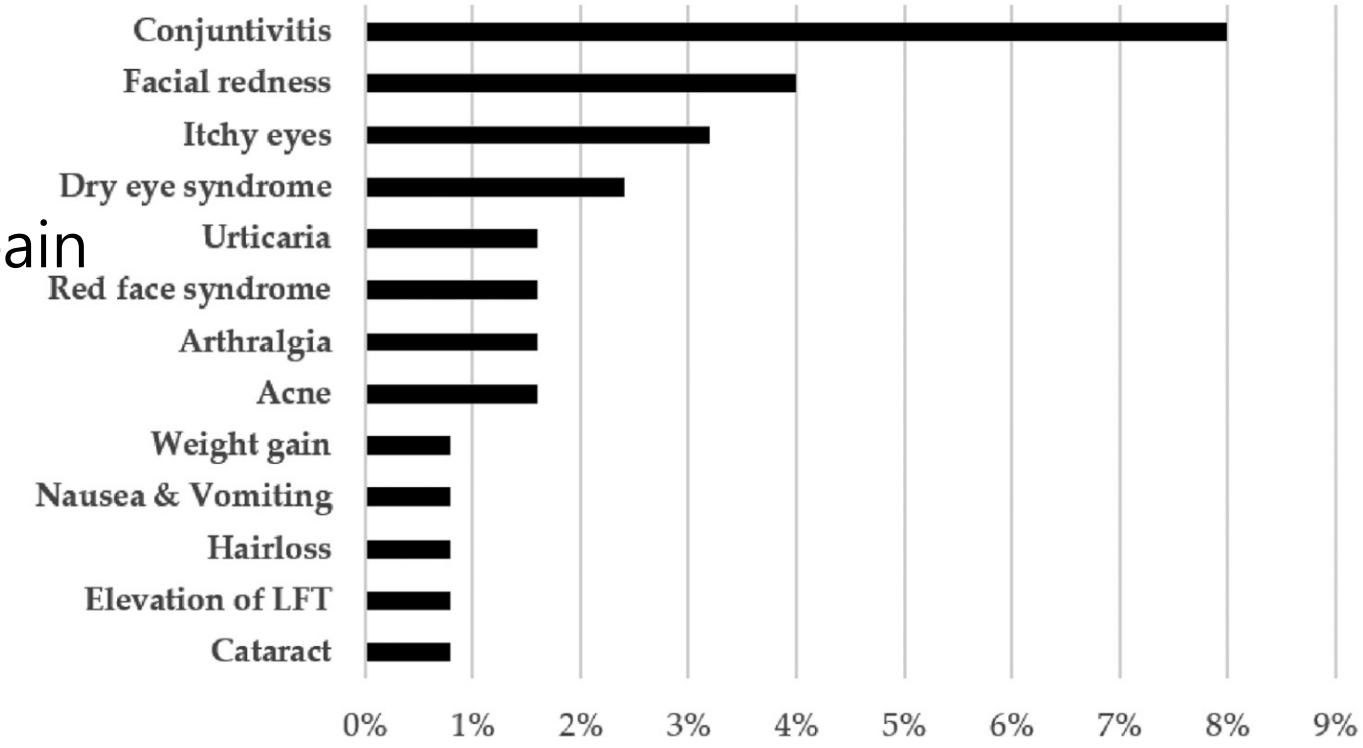


Figure 1. Adverse effects about dupilumab.

Conjunctivitis incidence rate of Biologics in AD

- Dupilumab, tralokinumab, and lebrikizumab : all associated with higher rates of ocular adverse events
  - including conjunctivitis, blepharitis, keratitis, and dry eyes

- Incidence of conjunctivitis may be lower with tralokinumab than with dupilumab, though no head-to-head studies have been performed.

Dupilumab monotherapy*		**Dupilumab+TCS****		**Tralokinumab monotherapy***		**Tralokinumab +TCS****		**Lebrikizumab monotherapy***		**Lebrikizumab+TCS****	
Dupilumab 300mg Q2W N=529 n(%)	Placebo N=517 n (%)	Dupilumab 300mg Q2W+TCS N=110 n(%)	Placebo+TCS N=315 n (%)	Tralokinumab 300 mg Q2W N=1180 n(%)	Placebo N=388 n (%)	Tralokinumab 300 mg Q2W+TCS N=243 n(%)	Placebo+TCS N=123 n (%)	Lebrikizumab 250mg Q2W N=638 n(%)	Placebo N=338 n (%)	Lebrikizumab 250mg Q2W+TCS N=145 n(%)	Placebo+TCS N=66 n (%)
51 (10)	**12 (2)**	**10 (9)**	**15 (5)**	**88 (7.5)**	**12 (3.1)**	**33 (13.6)**	**6 (4.9)**	**61 (10)**	**10 (3)**	**7 (5)**	**0**
* Pooled analysis of SOLO 1, SOLO 2, and AD-1021. **Analysis of CHRONOS where subjects were on background TCS therapy. *** Conjunctivitis cluster includes conjunctivitis, allergic conjunctivitis, bacterial conjunctivitis, viral conjunctivitis, giant papillary conjunctivitis, eye irritation, and eye inflammation.		*Pooled analysis of ECZTRA 1 and ECZTRA 2. ** Analysis of ECZTRA 3 where subjects were on background TCS therapy. *** Conjunctivitis cluster includes conjunctivitis and allergic conjunctivitis.						* Integrated analysis of ADvocate 1, ADvocate 2, and the phase 2 dose finding trial (KGAF). ** Analysis of TCS concomitant therapy trial ADhere. *** Conjunctivitis cluster includes conjunctivitis, conjunctivitis allergic, and conjunctivitis bacterial.			

Paradoxical head and neck erythema

- **Dupilumab facial redness (DFR), Dupilumab facial dermatitis (DFR)**
- **DAHND (dupilumab-associated head and neck dermatitis)**

- 4 and 43.8%
  - 84.6% - pre-existing facial dermatitis
  - 15.4% (~48%) - new onset

(1) Drug related
  - adverse event due to dupilumab
    - hypersensitivity reaction to dupilumab
    - pronounced type 22 immune signature mediated by oligoclonally expanded T cells
  - steroid withdrawal
  - TCI related flushing

(2) Site-specific treatment failure – photosensitivity

(3) Seborrheic dermatitis–like reaction to facial *Malassezia* species

(4) Demodex proliferation related rosacea

(5) Paradoxical flaring of allergic contact dermatitis

Dupilumab facial redness (DFR)

(1) Drug related

(2) Site-specific treatment failure (25%)

(3) Seborrheic dermatitis–like reaction to facial *Malassezia* species
- HND - *Malassezia* hypersensitivity
  → Itraconazole try

(4) Paradoxical flaring of ACD
- ACD fragrance → Patch test (esp, eyelid involve)

(5) Unopposed activation of Th1 and/or Th17
- Psoriasiform dermatitis
- Rosacea (or TCS / TCI) – oral TC
  - Demodex folliculitis
  - Rosacea-like folliculitis : 6.4%

Spontaneous resolution was observed with no treatment discontinuation

Vs.

Switching to JAKi

J Eur Acad Dermatol Venereol. 2023;37:e300-e302.

J Dermatolog Treat. 2023;34:2242540.

Biologics

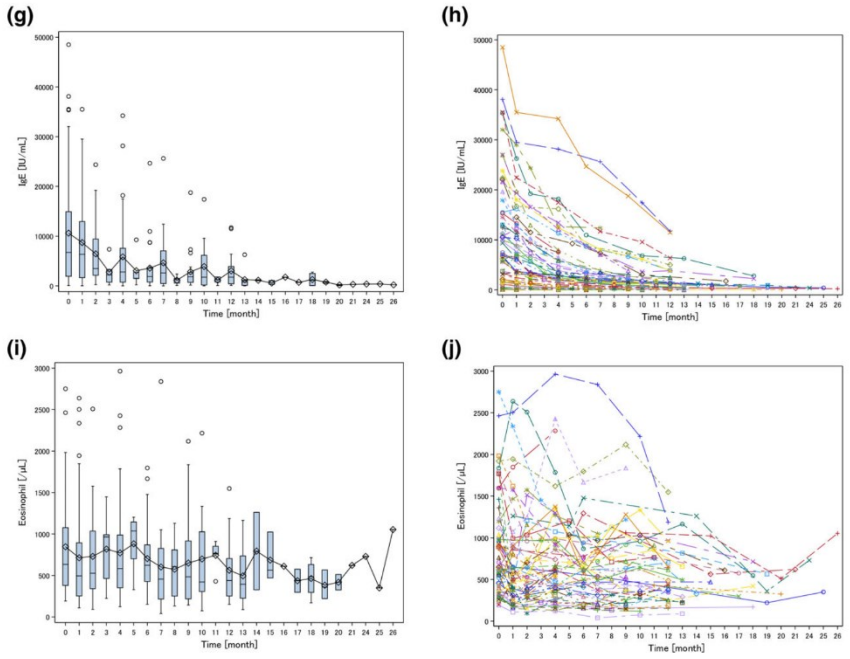
GUIDELINE

European guideline (EuroGuiDerm) on atopic eczema: part I – systemic therapy

Biologics

Monitoring No biochemicals or instrumental exams are reported to be required for the monitoring of the therapy.

- Transient eosinophilic surge
- IgE 감소

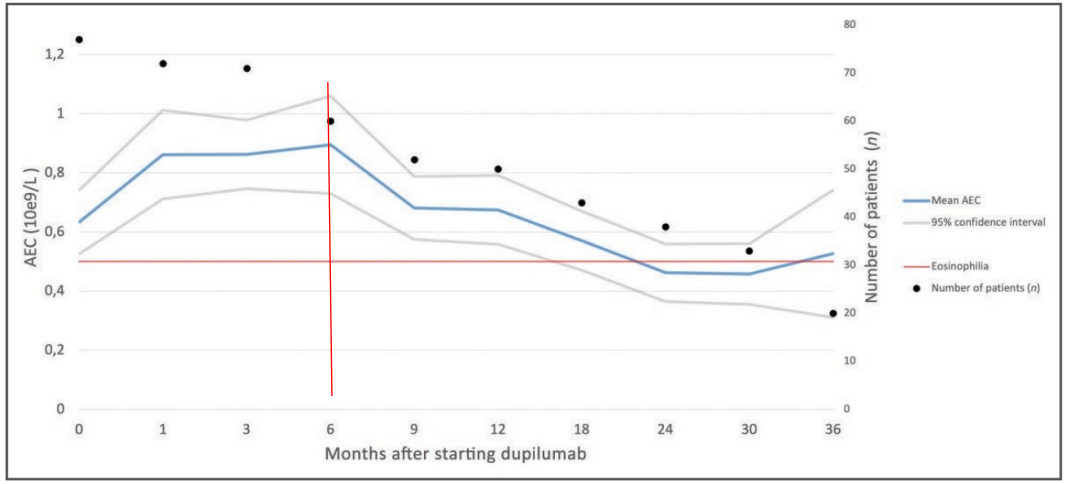


JEADV 2022;36:1409–1431

Australasian Journal of Dermatology 2021;62:e504–e509

Dupi → Hypereosinophilia

- Definition :
  - absolute eosinophil count (AEC) ≥ 1,500/mml on at least 2 different occasions in a 1 month interval
    - mild (500–1,500/mm^c)
    - moderate (1,500 to 5,000/mm^c)
    - severe (> 5,000/mm^c)
- Severe <2%, eosinophilia > 3,000/mm^c in from 4% to 14% of patients
- Onset : 4 days to 5 months
  - most cases occurring after more than 1 month
- Transient peripheral (hyper) eosinophilia
  - due to blocking eosinophil migration from blood into tissue



Dupi → Eosinophilia

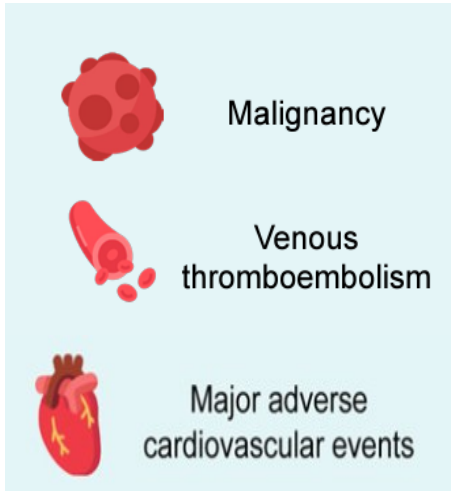
- **Netherlands single-center cohort study**
  - 38.5% (77/200) experiencing (hyper)eosinophilia
  - hypereosinophilia : 7.5%
    - 0.5% (one patient) had to discontinue dupilumab due to hypereosinophilia
  - predominantly male (62.3%)
  - median dupilumab treatment span : 21 months (range 1–58 months)

- Transient initial eosinophil surge, which was not clinically significant for most, regardless of their baseline eosinophilia status.

- Continuous routine monitoring is not recommended.
  - However, an AEC check in the first 6 months is advised. If AEC exceeds $5\times10^{9}L^{-1}$ or $3\times10^{9}L^{-1}$ twice, consultation with an internist, haematologist or paediatrician is advised.
  - Clinicians should inquire about symptoms of hyper-eosinophilic organ damage due to eosinophil accumulation in organs, which can include cardiac dysfunction, stroke, thromboembolic events, vasculitis, neurological symptoms in extremities and shortness of breath.

Br J Dermatol 2024;00:1–2

Screening of JAK inhibitors

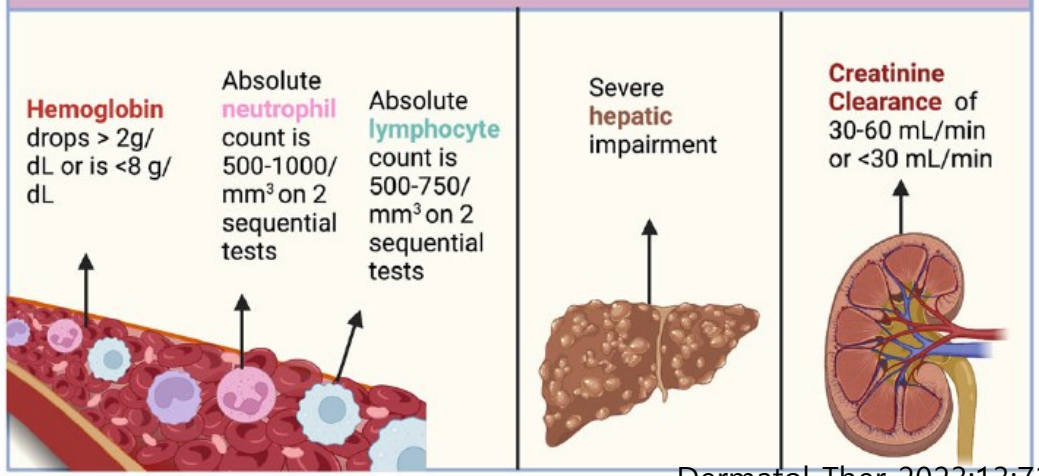


Initial Screening	1 Month	3 Months	Every 3-6 Months*
Age > 65 Smoking Use of oral contraceptives/ hormone replacement Risk and/or hx of hepatitis B and C Tuberculosis Cardiovascular disease Pregnancy and/or lactation Vaccination status Risk and/or hx of thromboembolism and blood clotting disorder Malignancy	✓ Complete blood count with a differential ✓ Liver transaminases ✓ Kidney function tests	✓ Complete blood count with a differential ✓ Liver transaminases ✓ Kidney function tests ✓ Lipid panel	✓ Complete blood count with a differential ✓ Liver transaminases ✓ Kidney function tests

Baseline Lab Tests

- Complete blood count with a differential
- Liver and kidney function tests
- Tuberculosis test
- Hepatitis B & C panel
- Baseline lipid panel
- Pregnancy test (if applicable)

Consider dose reduction or temporary cessation if:



Dermatol Ther 2023;13:729–749

Nine specified risk factors - ABCDHM

- Age 65 years or older
- history of Atherosclerotic cardiovascular disease (ASCVD), VTE
- Body mass index (BMI) 30 kg/m^2 or greater
- Current smoking
- Diabetes mellitus
- Dyslipidemia
  - high-density lipoprotein (HDL) cholesterol less than 40 mg/dL
- **H**ypertension
- history of Malignancy
- poor Mobility
  - severe mobility impairment on the EuroQol-5 Dimension (EQ-5D)

Special interest for JAKi

RA - 69.5%
AD - 52.1%
AA - 50.6%

Adv Ther. 2023;20;1-17

Table 1 Proportion of patients with each of the specified risk factors at baseline from RCT

	RA *N* = 3770, PYR = 14,744	AD *N* = 2636, PYR = 4628	AA *N* = 1303, PYR = 1868
ASCVD	119 (3.2)	25 (0.9)	12 (0.9)
Current smoker	603 (16.0)	634 (24.1)	222 (17.0)
Hypertension	1348 (35.8)	349 (13.2)	145 (11.1)
HDL < 40 mg/dL	308 (8.2)	360 (13.7)	116 (8.9)
Diabetes mellitus	335 (8.9)	71 (2.7)	40 (3.1)
≥ 65 years[a]	632 (16.8)	101 (3.8)	6 (0.5)
BMI ≥ 30 kg/m^2	1100 (29.2)	496 (18.8)	266 (20.4)
History of malignancy	52 (1.4)	27 (1.0)	17 (1.3)
Severe mobility impairment (EQ-5D)[b]	468 (12.4)	51 (1.9)	4 (0.3)
Any of 9 risk factors[c]	2619 (69.5)	1373 (52.1)	659 (50.6)

Data are *n* (%)

AA alopecia areata; *AD* atopic dermatitis; *ASCVD* atherosclerotic cardiovascular disease; *BMI* body mass index; *CV* cardiovascular; *EQ-5D* EuroQol-5 dimension; *HDL* high-density lipoprotein; *MACE* major adverse cerebrocardiovascular event; *MI* myocardial infarction; *N* number of patients in analysis population; *n* number of patients in the specified category; *PYR* patient-years of exposure for risk; *RA* rheumatoid arthritis

[a]The age of participants in AA clinical trials was limited to 60 years or younger for males and 70 years or younger for females to reduce concomitant androgenic alopecia

[b]Severe mobility impairment indicated by a response of either 'I have severe problems in walking about' or 'I am unable to walk about'

[c]ASCVD, current or past smoking (past smoking was not systematically documented in all trials), hypertension, HDL cholesterol < 40 mg/dL, diabetes mellitus, age 65 years or older, BMI ≥ 30 kg/m^2, history of malignancy, and severe mobility impairment at EQ-5D baseline

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Janus Kinase Inhibitor Boxed Warning

Statement from the American College of Rheumatology
Updated: January 28, 2022

- ✓ ORALSURV (FDA-mandated post-marketing phase IIIb–IV study)
  - ✓ enrolled 4,362 patients with **RA aged >50 years** who had **at least one cardiovascular risk factor**
  - ✓ additional cardiovascular (CV) risk factor (current cigarette smoking, hypertension, hypercholesterolaemia, diabetes mellitus, family history of premature coronary heart disease, extra-articular disease associated with RA, history of coronary artery disease)
- ✓ Patients on background methotrexate therapy were randomly allocated to receive treatment either with tofacitinib at a dose of 5mg or 10mg twice daily or with a TNF inhibitor (etanercept or adalimumab, depending on the region)

Table 1 Oral Surveillance: adjudicated MACE, malignancies and VTE [3]

EVENT *Hazard Ratio (HR)* *Tofacitinib vs TNFi* *(Confidence Interval)*	**Tofacitinib 5 mg BID** (N=1455)	**Tofacitinib 10 mg BID** (N=1456)	**TNFi** **adalimumab 40mg q 14 days** **-OR-** **etanercept 50mg q 7 days** (N=1451)
MACE *(All fatal CV events, non-fatal MI, or non-fatal CVA)*	1.24 (0.81, 1.91)	1.43 (0.94, 2.18)	Referent
Pulmonary embolism	2.93 (0.79-10.83)	8.26 (2.49-27.43)	Referent
DVT	1.54 (0.60-3.97)	2.21 (0.90-5.43)	Referent
VTE	1.66 (0.76-3.63)	3.52 (1.74-7.12)	Referent
Malignancy *(all non-melanoma cancer)*	1.47 (1.00, 2.18)	1.48 (1.00, 2.19)	Referent
Non-melanoma Skin Cancer	1.90 (1.04-3.47)	2.16 (1.19-3.92)	Referent
Death from any cause	1.49 (0.81-2.74)	2.37 (1.34-4.18)	Referent

Serious adverse events - Black box warning of JAKi

TABLE 2 Lower risk for major cardiovascular events and venous thrombolism under therapy with janus kinase inhibitors in patients with atopic dermatitis compared to rheumatoid arthritis.

Incidence rates per 100 patient-years		Baricitinib	Upadacitinib	Abrocitinib	Tofacitinib	Underlying risk of the disease population untreated with JAKi
MACE	AD	0.09 [0.0–0.3][46,64]	≤0.1[104]	0.18 [0.04–0.52][105]	NA	0.15–0.62[64]
	RA	0.5 [0.4–0.64][64]	0.6–1.0[104]	NA	0.9–1.0[113]	0.27–3.2[64]
VTE	AD	0.09 [0.0–0.3][46,64]	≤0.1[104]	0.30[105]	NA	0.18–0.24[64]
	RA	0.49 [0.38–0.61][64]	0.4–0.5[104]	NA	0.3–0.7[113]	0.33–0.79[64]

JAKi trials in AD demonstrate lower rates of VTE than in RA trials, and these VTEs occurred predominately in patients with pre-existing risk factors and at higher doses

Risk factors

MACE

- history of previous myocardial infarction or stroke
- old age
- smoker and aspirin users

VTE

- history of VTE
- age>65 years
- history of inherited thrombophilias (e.g. factor V Leiden)
- exogenous estrogen use
- recent surgery
- immobility
- uncontrolled hypertension
- obesity
- current or prior tobacco use
- cancer
- pregnancy
- concomitant IMIDs

Benefits and risks should be discussed with every patient when prescribing JAKi

→ Annually recheck!

Malignancy risk (except NMSC)

- AD does not appear to be associated with most cancers
  - may be a slight increased risk for non-Hodgkin lymphoma
- While JAK2 inhibitors are used to treat certain myeloproliferative neoplasms, treating IMIDs with JAKi may be associated with lymphoma or solid tumor development

- Baricitinib in AD – 0.22/100 PYs vs. 0.66/100 PYs in the placebo-controlled group
- Upadacitinib - 0.1/100 PYs at 15mg and 0.5/100 PYs at the 30mg
- Abrocitinib - 0.1/100 PYs

TABLE 3.

Comparison of the Presence of Boxed Warnings for JAK Inhibitors and Traditional Systemic Immunosuppressive Therapies

Drug	Boxed Warning?	Warnings
Upadacitinib	Yes	MACE, malignancies, VTE, infection
Abrocitinib	Yes	MACE, malignancies, VTE, infection
Methotrexate	Yes	Fetal death, teratogenicity, malignancy, infection, liver toxicity, pulmonary toxicity, hemorrhagic enteritis, tumor lysis syndrome, severe adverse cutaneous reactions
Cyclosporine	Yes	Malignancy, infection, hypertension, renal toxicity

TABLE 2.

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[i]	--	--	Khan, N., et al[20]
	--	--	7.6[j]	--	Wei, L., et al[21]
	--	--	--	0.02[k]	Huerta, C., et al[22]

J Drugs Dermatol. 2022;21:1298-1303

Common adverse event of JAKi

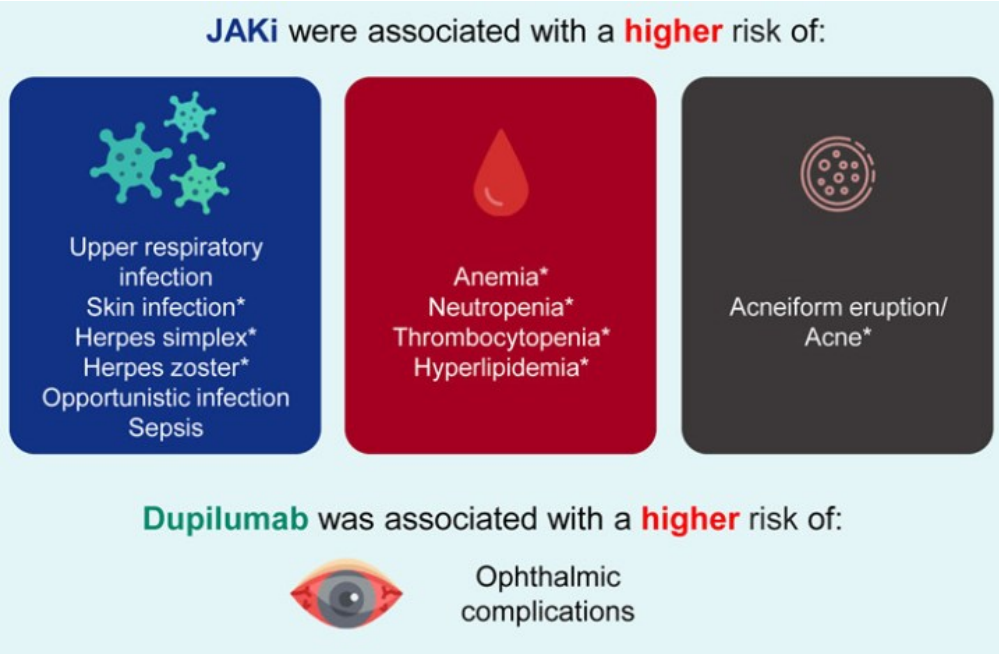


Table 2. Incidence of AEs of Interest in Patients with Atopic Dermatitis Treated with Jak Inhibitors (Events per 100 Patient-y)

	Baricitinib 2 mg/4 mg Pooled	Abrocitinib 100 mg	Abrocitinib 200 mg	Upadacitinib 15 mg	Upadacitinib 30 mg
Number of patients	2,531	1,023	2,105	1,239	1,246
Person-y	2,247	849.9	1,238.9	1,373.4	1,414.2
Duration of exposure (days)	310 (median)	ND	ND	405 (mean)	415 (mean)
Severe AEs	ND	ND	ND	12.4	15.2
Serious AEs	6.1	6.7	7.1	7.1	7.7
AEs leading to discontinuation	4.6	10.9	14.3	4.4	5.7
Herpes zoster (global population)	2.3	2.1	4.3	3.5	5.2
Oral herpes/herpes simplex	4.9/4.0	ND/7.1	ND/11.1	5.0/ND	8.8/ND
Acne/Folliculitis	ND/3.2	4.9/ND	13.1/ND	13.3/3.7	20.2/4.1
Headache	7.6	7.5	16.7	7.4	6.6
Nausea	2.1	7.3	30.7	3.0	3.1
Vomit	ND	2.9	6.3	ND	ND
CPK elevation	2.1 (≥10 × ULN)	5.3	7.5	7.1	10.8
Anemia	0.9 (<10 mg/dl), 0 (<8 mg/dl)	0.8	4.8	1.3	3.3
Neutropenia	0.2 (<1000 cells/mm^3)	0.1	1.2	1.8	3.2
Lymphopenia	1.0 (<500 cells/mm^3)	0.6	2.1	0.4	0.6
Thrombocytopenia	1.0 (>600 billions/l)	0.2	4.1	ND	ND
Pancytopenia	ND	0.1	0.2	ND	ND
Hepatic disorders	Few[1]	2.8	4.5	6.1	7.5
References	(Bieber et al., 2021b)	(Pharmaceuticals_and_Medical_ Devices_Agency, 2021b)		(Guttman-Yassky et al., 2023)	

Abbreviations: AE, adverse event; CPK, creatine kinase; ND, not described; ULN, upper level of normal.
[1]The number was not described.

JID Innovations 2023;3:100195

Common adverse event of JAKi

Nausea

- 7-20% (abrocitinib)
- Most cases of nausea occurred in women within the first week of treatment and resolved after a median of 15 days

Acne

- Up to 17%
- highest for upadacitinib 30mg
- lowest for baricitinib
- Patients who develop acne generally respond well to common acne treatments.

Lab. monitoring

Table 1 Laboratory and vaccine monitoring recommendations for Janus kinase inhibitor treatment of atopic dermatitis

	Pretreatment	4–12 weeks after initiation[a]	Every 3–6 months
TB screening[b]	×		
Pregnancy[c]	×	×	×
HBV[d]/HCV	×		
HIV[e]	×		
CBC with differential	×	×	×
CMP	×	×	×
HDL cholesterol, LDL-cholesterol, TG	×	×	Annually
Vaccination	Comments		
Inactivated pneumococcal vaccine	Recommended for patients aged > 18 years		
Influenza	Recommended annually		
Shingrix – recombinant zoster vaccine	Recommended for patients aged > 18 years; two doses separated by 2–6 months		

A practical guide to using oral Janus kinase inhibitors for atopic dermatitis from the International Eczema Council
Br J Dermatol 2025;192:135–143

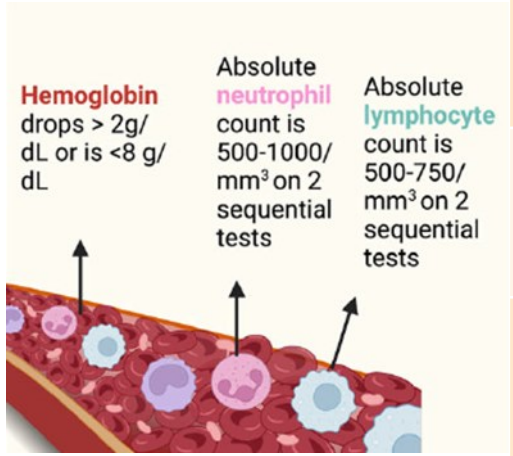
Hematological changes associated with JAKi

Rheumatology. 2024;63:298-308

	Platelet counts	Neutrophil counts	Lymphocyte counts	Hemoglobin levels
Abrocitinib	Transient ↓	No change	No change	No change
Upadacitinib	Small transient ↓	↓ in weeks 4–8 followed by stabilization at a lower value than baseline	Small transient ↑ up to week 36 ↓	No change ↓
Baricitinib	Transient ↑	↓	Transient ↑	Transient ↓

- Abrocitinib : reduced platelet counts
  - Highest at week 4 → ongoing abrocitinib : upward by week 12
- Baricitinib : Idiosyncratic platelet activation
  - tyrosine kinase inhibitors may activate procoagulant activity which might be related to changes in lipids or lipoprotein levels
- Decreased amounts of neutrophil (Neutropenia, 3.2%): more profound in **upadacitinib** 15 or 30 mg
- Although upadacitinib is a JAK1 selective inhibitor, research suggests JAK2 is dependent on JAK1 for transphosphorylation and activation; the intertwined pathways of JAKs could explain why neutropenia has been reported as an AE for upadacitinib

Contraindication



Abnormal laboratory findings

- ✓ 절대 호중구수(ANC) 1000 cells/mm^3 미만인 환자
- ✓ 절대 림프구수(ALC) 500 cells/mm^3 미만인 환자
- ✓ 헤모글로빈 수치 8g/dL 미만인 환자

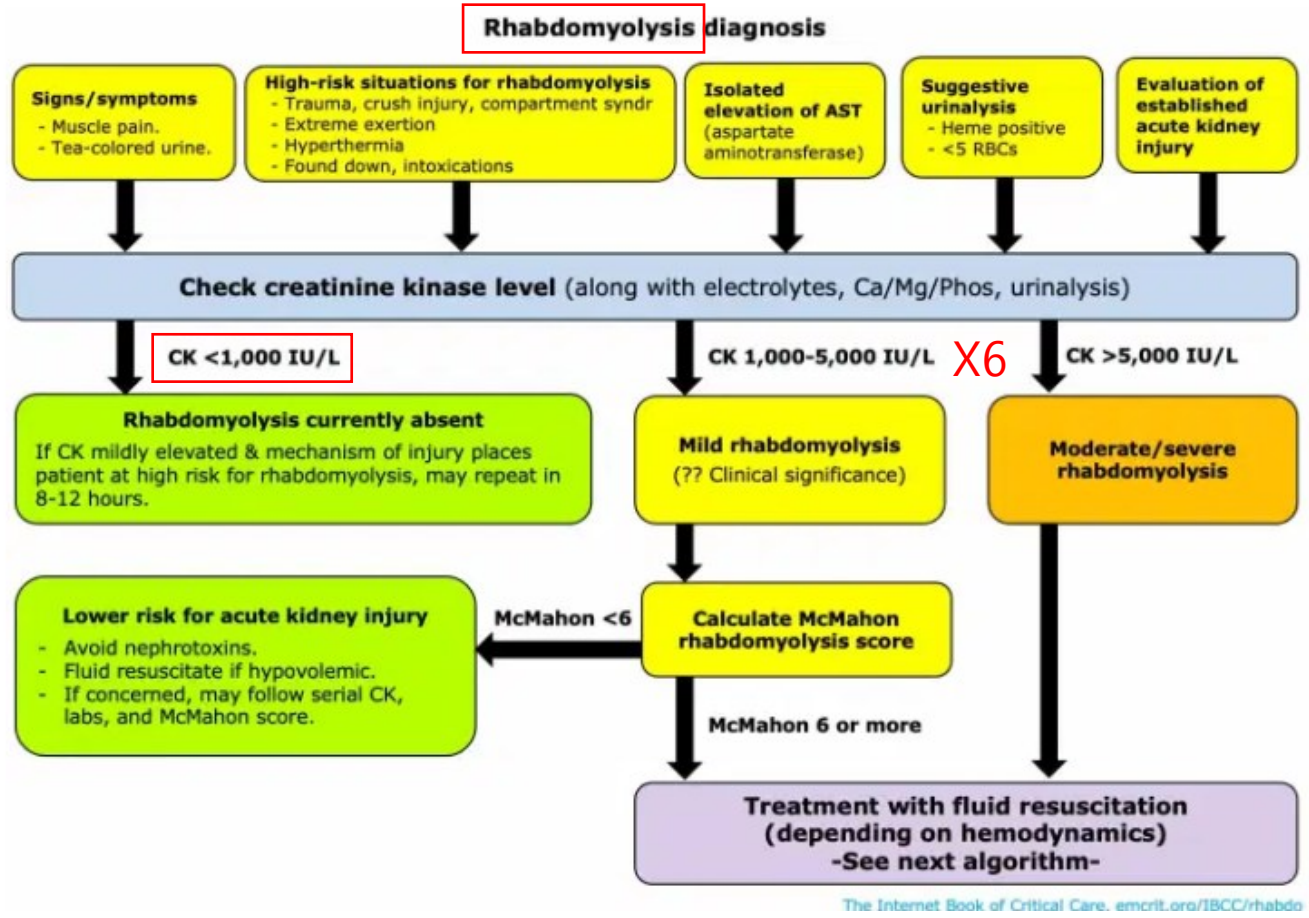
Agent	ANC	ALC	Hb	Platelet count	Hepatic function
Baricitinib (Olumiant®)	**<1,000 cells/ul**	**<500 cells/ul**	**<8g/dl**	-	**If DILI*** suspected
Upadacitinib (Rinvoq®)					
Abrocitinib (Cibinqo®)				**< 50,000/ul**	-

* DILI : Drug-induced liver injury

✓ May be restarted once ANC,ALC,Hb returns to normal range and no liver injury is checked

Lab monitoring – CPK elevation

- Exercise? (Skeletal Muscle origin)



Clin Rheumatol. 2020;39:613–4

- **Dose-dependently** increased among those treated with upadacitinib, abrocitinib, and baricitinib
- In most cases, these were **asymptomatic**, mild to moderate
- **Male** gender and **younger age** as significant risk factors for CK elevations ≥ 3 × ULN and ≥ 5 × ULN

Monitoring recommendations from expert panel in Canada (2024)

Dermatol Ther (Heidelb)
https://doi.org/10.1007/s13555-024-01243-8

PRACTICAL APPROACH

Practical Recommendations on Laborato Monitoring in Patients with Atopic Derm on Oral JAK Inhibitors

Mark G. Kirchhof · Vimal H. Prajapati · Melinda Gooderham · Chih-ho
Charles W. Lynde · Catherine Maari · Irina Turchin · Kim A. Papp

Table 4 Consensus recommendations and level of agreement

Recommendation statement	Median level of agreement	Range (mininum, maximum)
1. Routine assessment and monitoring of creatine phosphokinase (CPK) levels in patients with atopic dermatitis (AD) receiving oral Janus kinase inhibitor (JAKi) treatment is not recommended	100	90, 100
2. Unless observed changes in laboratory values between baseline and Weeks 8 and 12 are clinically meaningful, ongoing laboratory monitoring of patients with AD receiving oral JAKi treatment is generally unnecessary	80	59, 100
3. Dose reduction or switching oral JAKi treatment for patients with AD in response to meaningfully altered lipid levels may result in improvement in lipid levels	90	75, 100
4. In patients with AD receiving oral JAKi treatment, profound changes in laboratory parameters that reverse upon treatment discontinuation are likely to recur on treatment re-initiation; therefore, alternative treatment options, including an oral JAKi that does not result in the same risk profile or treatments other than oral JAKi, might be considered	97	80, 100

AD atopic dermatitis, *CPK* creatine phosphokinase, *JAKi* Janus kinase inhibitor

International Eczema Council

In general, monitoring CPK levels during treatment with JAKi is not recommended.

In case of clinical symptoms (e.g. muscle weakness and/or myalgia), CPK levels should be measured

Br J Dermatol 2025; **00**:1–2
https://doi.org/10.1093/bjd/ljae485
Advance access publication date: 13 December 2024

Comment on 'A practical guide to using oral Janus kinase inhibitors for atopic dermatitis from the International Eczema Council': a case of rhabdomyolysis induced by upadacitinib

- 23/M, jet ski, upa 15mg
- 30/M, CrossFit, upa 30mg
- 2 boys - Upadacitinib in Adolescents With Moderate to Severe Atopic Dermatitis Analysis of 3 Phase 3 RCT

Table 1 Blood test results during admission and at follow-up. Day 0 indicates the day of presentation and admission to the hospital

Day	Hb (g dL−1) (RR 13.00–18.00)	Creatinine (mg dL−1) (RR 0.73–1.18)	Myoglobin (ng mL−1) (RR < 154.90)	Creatinine kinase (IU L) (RR 30.0–200.0)	Lactate dehydrogenase (U L−1) (RR 125.0–220.0)	AST (U L−1) (RR 5.0–34.0)	ALT (U L−1) (RR 0.0–55.0)
Day 0	14.6	1.04	189.50	28616.0	546.0	552.0	431.0
Day 1	13.9	1.24	86.40	14204.0	NA	317.0	328.0
Day 3	12.9	1.04	NA	5071.0	192.0	128.0	222.0
Day 5	12.8	1.07	NA	2293.0	NA	67.0	167.0
Day 6	12.7	1.10	41.50	1681.0	NA	55.0	145.0
Day 9	14.0	1.13	29.30	580.0	NA	34.0	108.0

ALT, alanine transaminase; AST, aspartate transaminase; Hb, haemoglobin; NA, not available; RR, reference range.

신기능, 간기능 관련 용량 권고사항

	Renal impairment			**Hepatic impairment**			**Preconception period**
	Mild	Moderate	Severe	Mild (Child Pugh A)	Moderate (Child Pugh B)	Severe (Child Pugh C)	
Upadacitinib	OK	OK	15mg QD	OK	OK	X	1 month
Abrocitinib	OK	100 or 50 mg QD	50 mg QD (max 100mg QD)	OK	OK	X	1 month
Baricitinib	OK	2mg QD	X	OK	OK	X	1 month
Dupilumab	OK			OK			At least 3 months

린버크 제품설명서, 시빈코 제품설명서, 올루미언트 제품설명서, 듀피젠트 제품설명서 참조 accessed on Oct 4th 2024

Concomitant drug medication

- Immunosuppressive drug
  → Biologics
- Taking drugs with known interactions with JAKi
  → dupilumab or tralokinumab should be preferred

Drug	Main	Minor		Elimination	Half-life
Biologics	Dupilumab appears to have little effect on CYP450 activity.			Not been characterized degraded via catabolic pathways in the same manner as endogenous IgG.	~22~25 days
Baricitinib	CYP3A4 (in liver)	OAT3 BCRP	Probenecid	- Renal elimination is principal - Unchanged : Urine(75%), feces(20%) - Metabolites : ~<10%	~13 hours
Upadacitinib	CYP3A4	CYP2D6	Ketoconazole Rifampicin	- Unchanged : urine(24%), feces(38%) - Metabolites : 34%	~8.8 hours
Abrocitinib	CYP2C19 (~53%) CYP2C9 (~30%)	CYP3A4 CYP2B6 OAT3	Fluconazole SSRI Rifampicin	- Unchanged : ~ <1% - Metabolites(into urine) : >95%	~5 hours

Drug interaction

- Baricitinib
  - with probenecid (uric-acid-excretion-promoting drug) → decreased to 2 mg
- Upadacitinib
  - CYP3A4 inhibitors (itraconazole, clarithromycin, etc.) : increase levels of Upa
  - CYP3A4 inducers (rifampicin, carbamazepine, etc.) : decrease levels of Upa
- Abrocitinib
  - CYP2C19 inhibitors (fluconazole, SSRI, TCA, PPI etc.) : increase levels of Abro
  - CYP2C19 or CYP2C9 inducers (rifampicin, etc) : decrease levels of Abro

✓When used in combination with corresponding strong CYP inhibitors, JAK inhibitors should be administered at a lower dose.

Drug interaction

- Abrocitinib
  - drugs as the substrate of P-glycoprotein (dabigatran etexilate: anti-thrombotic drug, digoxin...)
    - actions of these drugs may be enhanced → carefully monitoring
  - contraindicated with concomitant use of antiplatelet therapy (except for low-dose aspirin < 81 mg daily) during the first three months of treatment due to risk of thrombocytopenia

Biologics

Pros

- Safety
- more favorable safety profile than conventional therapies, with fewer immunosuppressive adverse events

Cons

- Cost
- Regular injection

Type II comorbidity

JAK inhibitors

Pros

- Needle-phobic patients
- Once-daily oral tablets
- Dose flexibility
  - low and high doses
- Rapid reduction in pruritus
- Cost (compared to biologics)

Cons

- Screened for chronic infections, including tuberculosis and hepatitis
- Other laboratory monitoring

- Multi-axis activation with Th22 and Th1 contribution (psoriasiform dermatitis…)
- Inflammation (arthritis…)

WHICH THERAPY FOR WHICH PATIENT?

1. Possibility of Adverse event
   - Latent TB, cancer, smoker → Biologics
   - Drug interaction → Biologics
   - Age : young children/ geriatric → Biologics

Safety issue
→ Biologics

   - Conjunctivitis/ facial dermatitis concern → JAKi
   - Acne, recurrent H.simplex, eczema herpeticum → Biologics

WHICH THERAPY FOR WHICH PATIENT?

2. Comorbidity
   - Type II comorbidity – asthma…
   - Autoimmune – Arthritis, IBD, Alopecia, Vitiligo, Pso

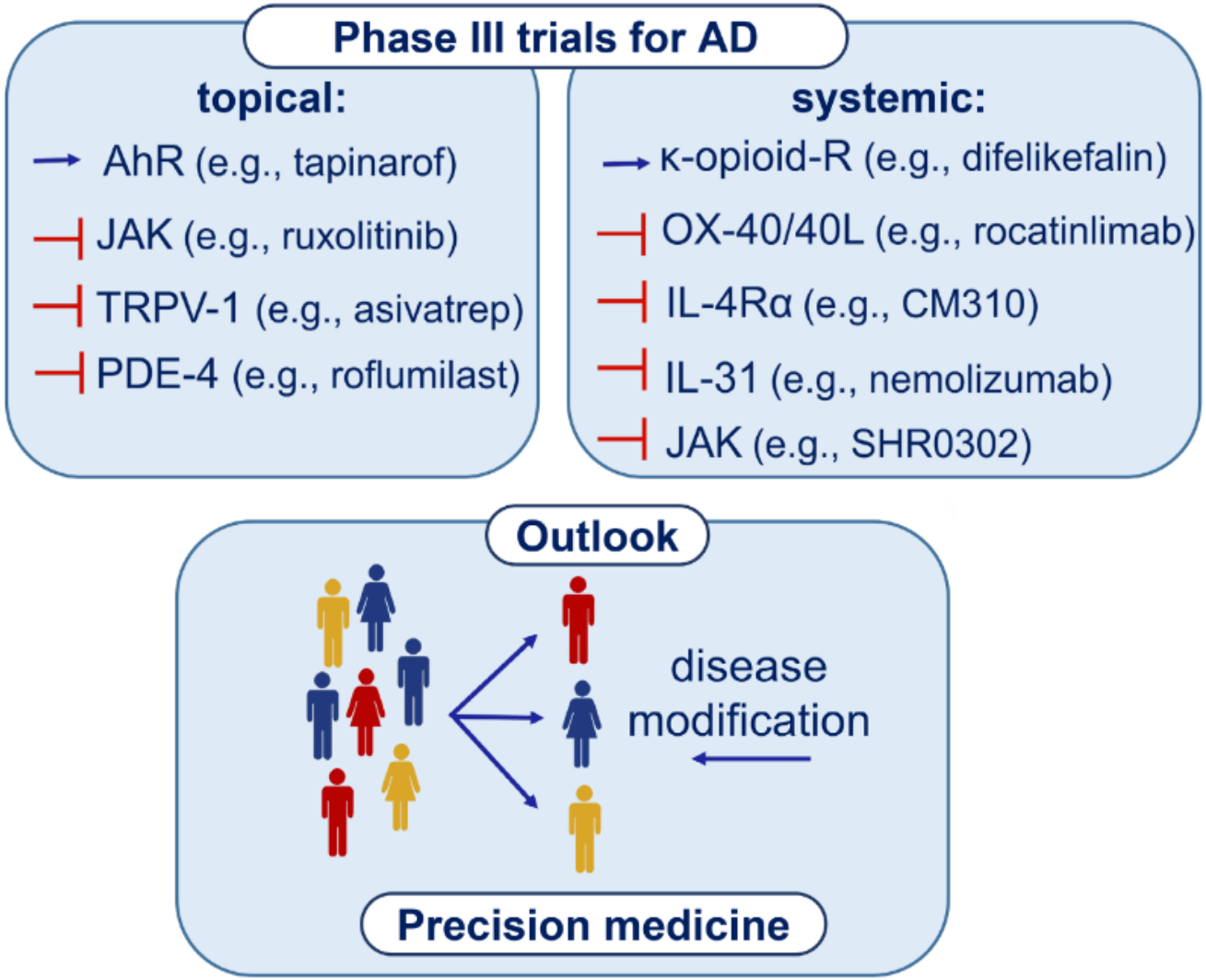
3. Patient preference
   - Needle phobia / storage issue
   - Cost

WHICH THERAPY FOR WHICH PATIENT?

4. Phenotype
   - Long-term continuous treatment of moderate severe AD
   - Intermittent Tx, more episodic
   - Severe pruritis with mild to moderate AD
   - Rapid induction - time sensitive life events, for example, upcoming weddings
   - Head and neck D / Hand and foot / genital and scalp pruritus…

Rapid action, flexibility
→ JAKi

Unveiling future therapeutic directions



- Episodic use of JAKi
- Long term of JAKi
- Dosing intervals for biologics
- Switching, Combination therapy
- When to Consider an Alternative Systemic Therapy
- Tapering and Discontinuation of Systemic Therapy
- Biomarker
- Disease modification
  - long term remission
  - Early intervention
  - Primary prevention
  - comorbidity