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PEER TO PEER TOOLKIT

A New Wave of Systemic Treatments: ATOPIC DERMATITIS, MEET JAK

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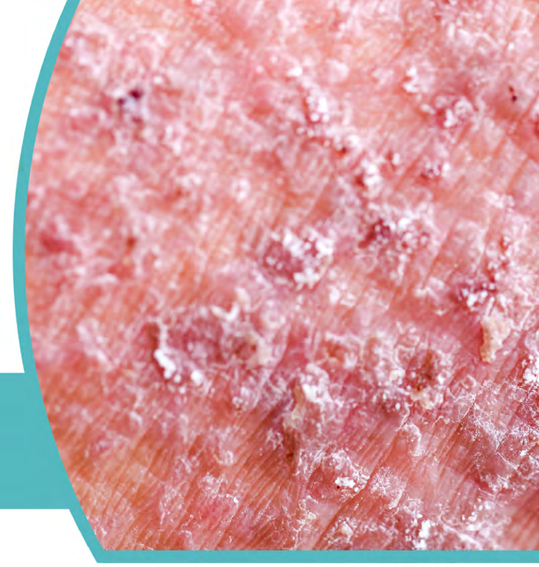
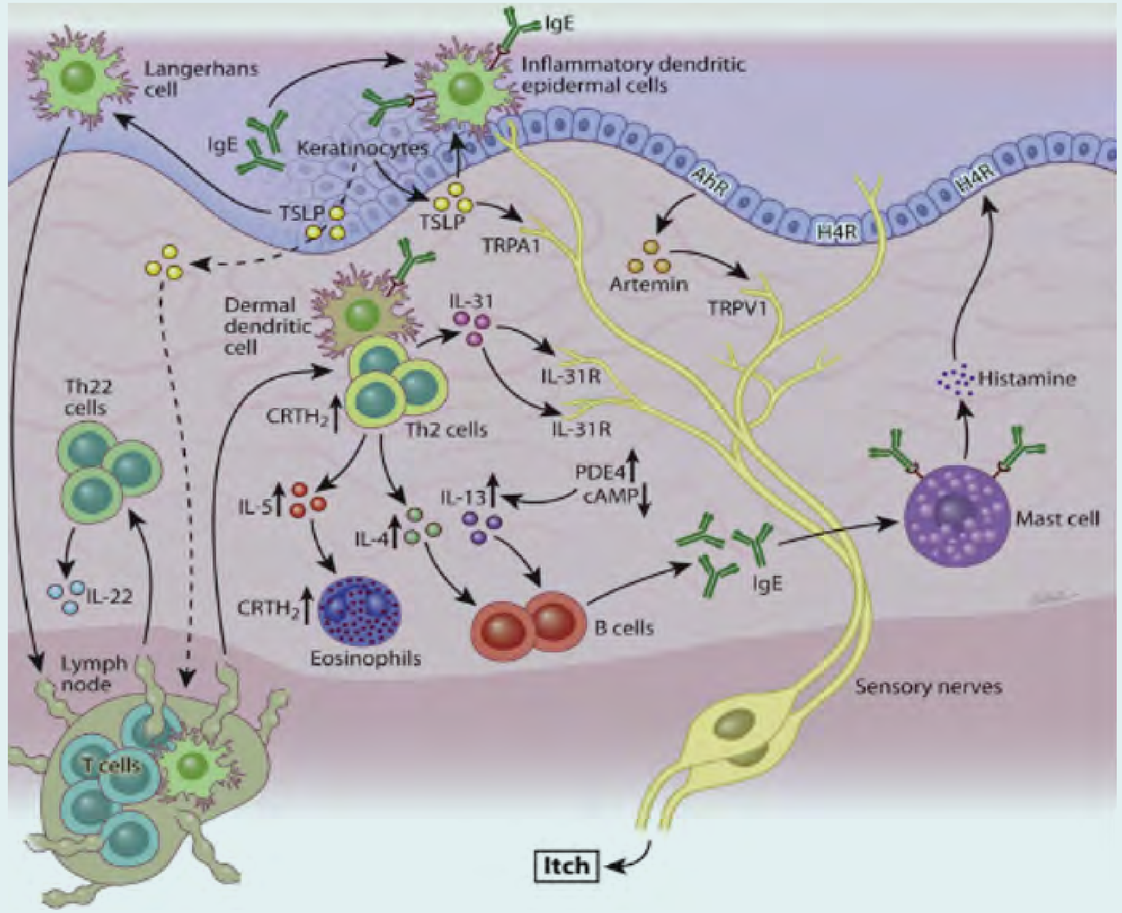


A New Wave of Systemic Treatments: Atopic Dermatitis, Meet JAK

THE BASICS OF ATOPIC DERMATITIS (AD)

AD IMMUNOPATHOGENESIS

IL-4, IL-13, IL-31, IL-5, TSLP, and IL-22 signal through the JAK-STAT pathway



CRTH2=chemoattractant receptor homologous molecules expressed on Th2 lymphocytes; IL=interleukin; TSLP=thymic stromal lymphopoietin;TRPA1=transient receptor potential A1; TRPV1=transient receptor potential cation channel subfamily V member 1.
Paller AS, et al. J Allergy Clin Immunol. 2017;140(3):633-643.

AD: DIAGNOSTIC FEATURES

- **ESSENTIAL FEATURES**; must be present:
  - Pruritus
  - Eczema (acute, subacute, chronic):
    - Typical morphology and age-specific patterns*
    - Chronic or relapsing history

  Patterns include:
  1) facial, neck, and extensor involvement in infants and children;
  2) current or prior flexural lesions in any age group;
  3) sparing of groin and axillary regions.

- **IMPORTANT FEATURES**; seen in most cases, adding support to the diagnosis:
  - Early age of onset
  - Atopy
    - Personal and/or family history
    - IgE reactivity
  - Xerosis

- **ASSOCIATED FEATURES** ; these clinical associations help to suggest the diagnosis of AD but are too non-specific to be used for defining or detecting AD for research and epidemiologic studies:
  - Atypical vascular responses (e.g., facial pallor, white dermographism, delayed blanch response)
  - Keratosis pilaris / pityriasis alba / hyperlinear palms / ichthyosis
  - Ocular / periorbital changes
  - Other regional findings (e.g., perioral changes / periauricular lesions)
  - Perifollicular accentuation / lichenification / prurigo lesions

- **EXCLUSIONARY CONDITIONS;** it should be noted that a diagnosis of AD depends on excluding conditions such as:
    - scabies
    - seborrheic dermatitis
    - contact dermatitis (irritant or allergic)
    - ichthyoses
    - cutaneous T-cell lymphoma
    - psoriasis
    - photosensitivity dermatoses
    - immune deficiency diseases
    - erythroderma of other causes

Eichenfield LF, et al. J Am Acad Dermatol. 2014;70:338-351.

ASSESSMENT OF AD SEVERITY

- Validated AD-specific severity scales
  - **SCORAD** (**SCOR**ing **A**topic **D**ermatitis index): includes extent, sleep, and itch
  - **EASI** (**E**czema **A**rea and **S**everity **I**ndex): includes extent
  - **IGA** (**I**nvestigator's **G**lobal **A**ssessment): simple 0- to 5-point scale
- Validated Patient Reported Outcome (PRO) measures
  - **POEM**, **P**atient-**O**riented **E**czema **M**easure
  - **DLQI**, **D**ermatology **L**ife **Q**uality **I**ndex;
  - **Pruritus NRS**, numerical rating scale

Siegfried EC, et al. Pediatr Dermatol. 2018;35:303-322. Chopra R, et al. Br J Dermatol. 2017;177:1316-1321. Silverberg JI, et al. Br J Dermatol. 2019;181:80-87.

AD MANAGEMENT ISSUES

IMPACT ON TREATMENT CHOICE

- Patient preference and ability
- Safety and efficacy
- Cost and access
- Comorbidities

THERAPEUTIC GOALS

- To reduce symptoms, prevent exacerbations and minimize therapeutic risks
- Prolonged remission and infrequent flares
  - Improved adherence through easy-to-use and simple, effective regimen
  - Improved QoL, including restful sleep and undisturbed activities of daily living

Retzler J, et al. Qual Life Res. 2019;28:2373-2381. Tollefson MM, Bruckner AL. Pediatrics. 2014;134:e1735-e1744. Weston WL, Howe W. Treatment of atopic dermatitis. 2020 (https://www.uptodate.com/contents/treatment-of-atopic-dermatitis-eczema).

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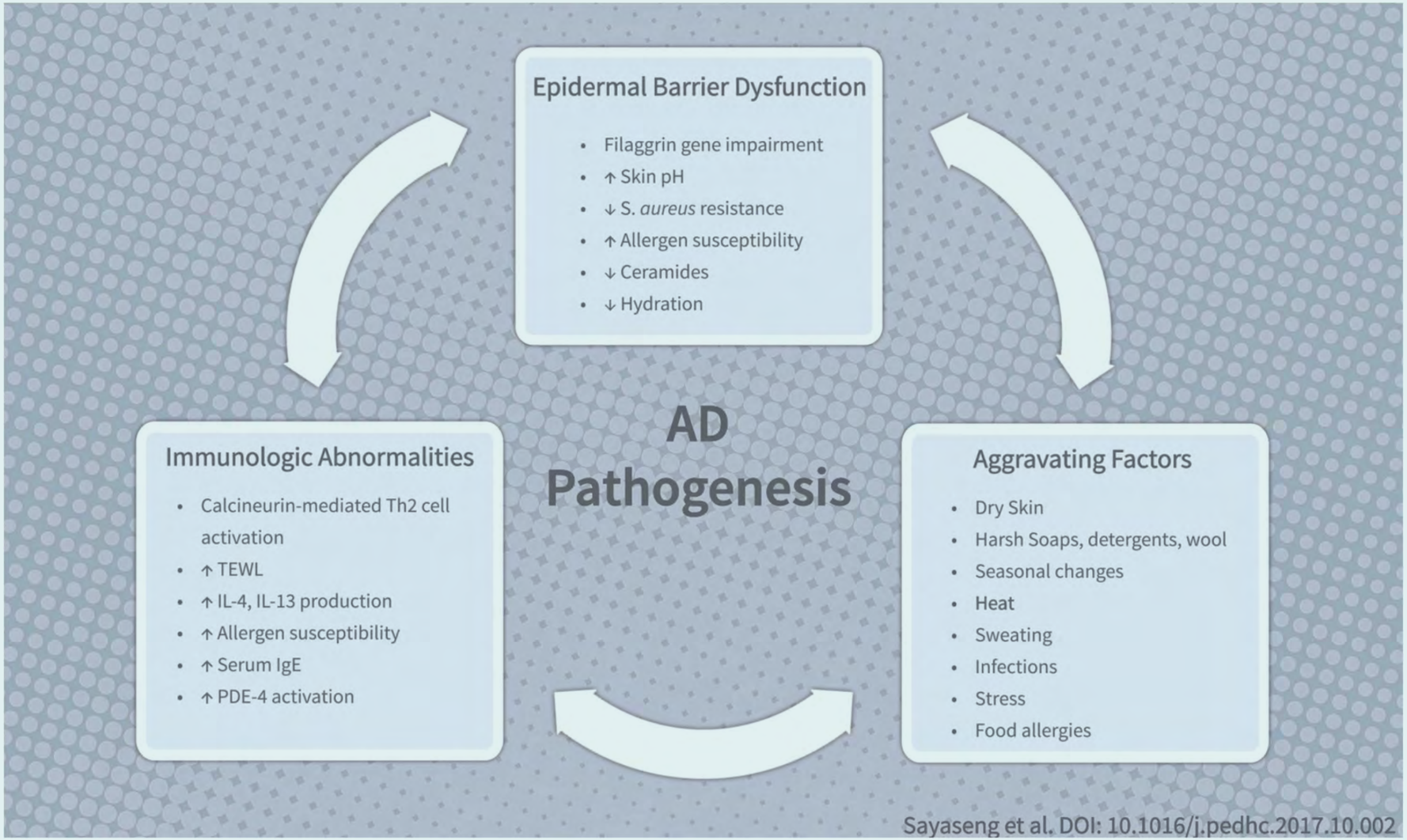

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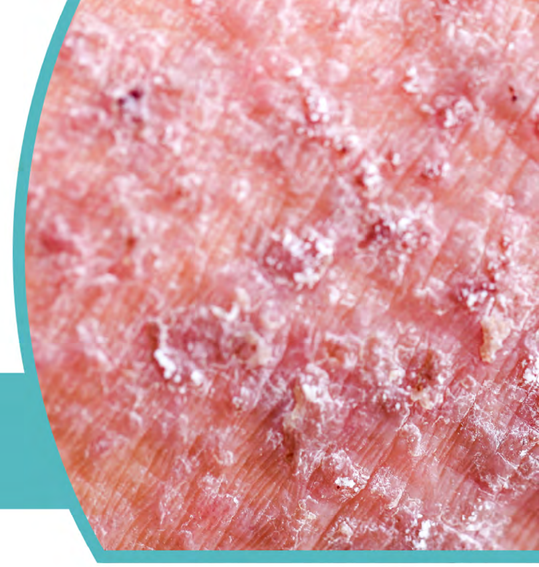


AD TREATMENT AND TRIAL DATA

AD MANAGEMENT

TOPICAL THERAPY

Limited BSA dermatitis

Non-targeted	**MORE** Targeted
• TCS • TCI	• Crisaborole ointment • Ruxolitinib 1.5% cream

SYSTEMIC THERAPY

- >10% BSA dermatitis
- Multifocal/diffuse pruritus
- Topical therapies ineffective

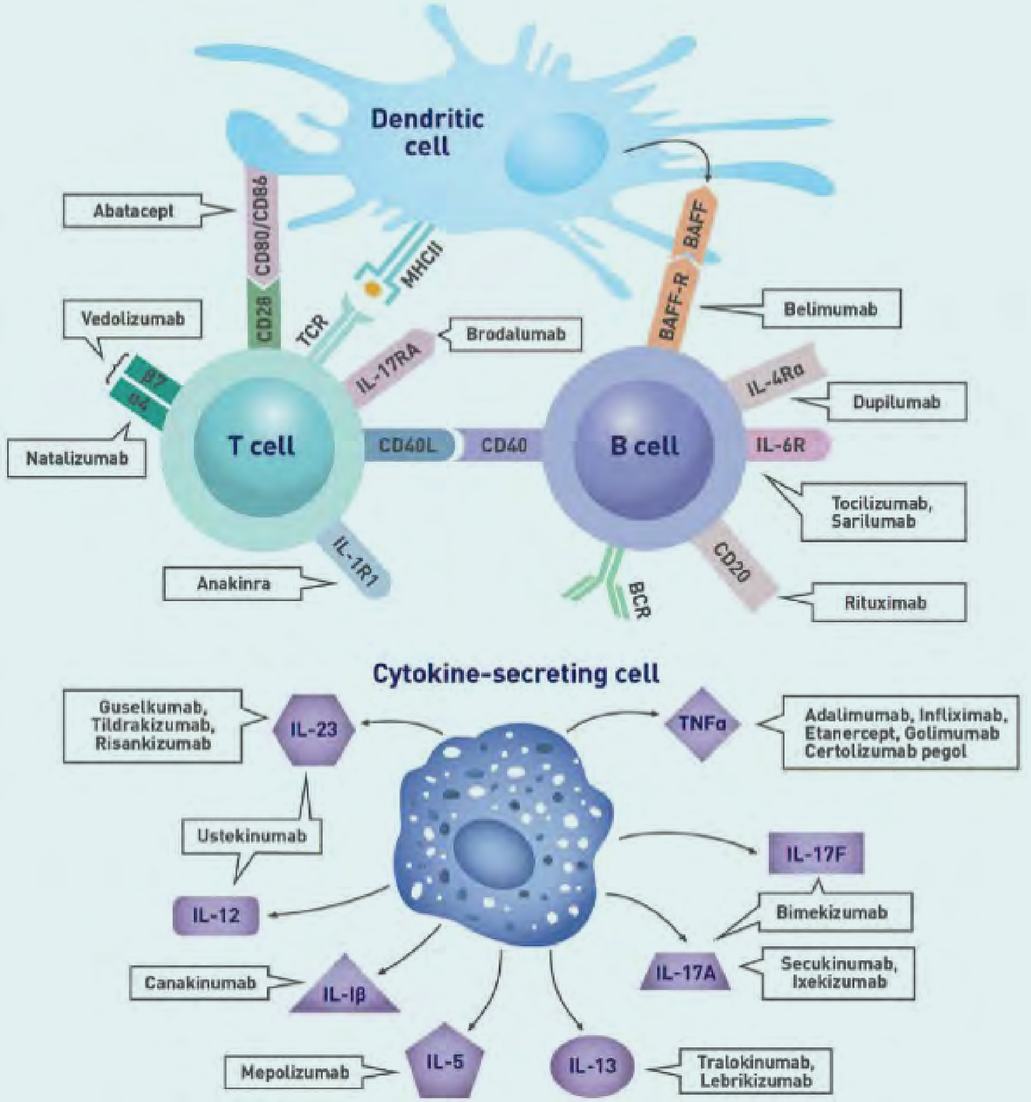
Non-targeted	**MORE** Targeted	Targeted

• Cyclosporine
• Methotrexate
• Azathioprine
• Mycophenolate
	• JAK inhibitors
	  • Baricitinib
	  • Abrocitinib
	  • Upadacitinib
		• Dupilumab
		• Tralokinumab
		• Lebrikizumab
		• Nemolizumab

SEVERITY →

TCS=topical corticosteroid, TCI=topical calcineurin inhibitor

JAKINIB
- DRUG DEPENDENT



Papp KA, Haraoui B, Kumar D, et al JCMS 2018

PHASE III TRIALS LEADING TO APPROVAL OF DUPILUMAB FOR AD

Moderate-to-severe AD (IGA score ≥3)

SOLO-1 & SOLO-2[1]
- N=1,379
- Adults (≥18 years old)

- Dupilumab 300 mg QW or Q2W
- No topical medication

CHRONOS[2]
- N=740
- Adults (≥18 years old)

- Dupilumab 300 mg QW or Q2W
- Topical medication given to all groups

LIBERTY AD ADOL[3]
- N=251
- Adolescents (12– <18 years old)

- Dupilumab 200 or 300 mg Q2W (wt-based), or 300 mg Q4W
- Topical treatment only as a rescue

Severe AD (IGA score 4)

LIBERTY AD PEDS[4]
- N=367
- Children (6–11 years old)

- Dupilumab 100 mg or 200 mg Q2W (wt-based), or 300 mg Q4W
- Topical corticosteroids given to all groups

IGA, investigator's global assessment.

1. Simpson EL, et al. N Engl J Med. 2016;375:2335–48; 2. Blauvelt A, et al. Lancet. 2017; 389:2287–303; 3. Simpson ET, et al. JAMA Dermatol. 2020;156:44–56;4. Paller AS, et al. J Am Acad Dermatol. 2020;83:1282–93.

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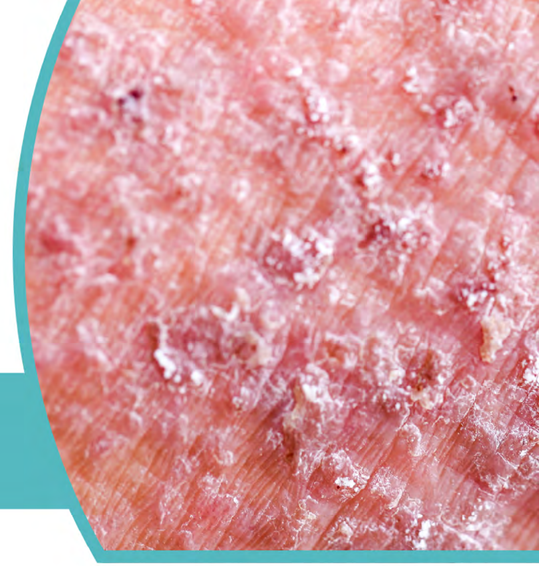

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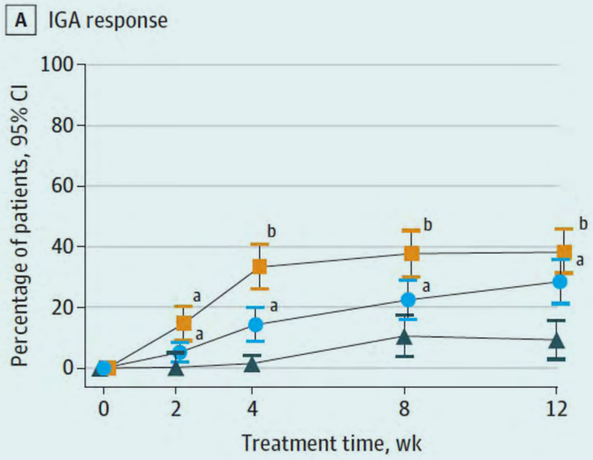
JAK INHIBITORS WITH PHASE 3 CLINICAL TRIAL DATA IN AD

- Ruxolitinib 1.5% cream
- Baricitinib
- Abrocitinib
- Upadacitinib

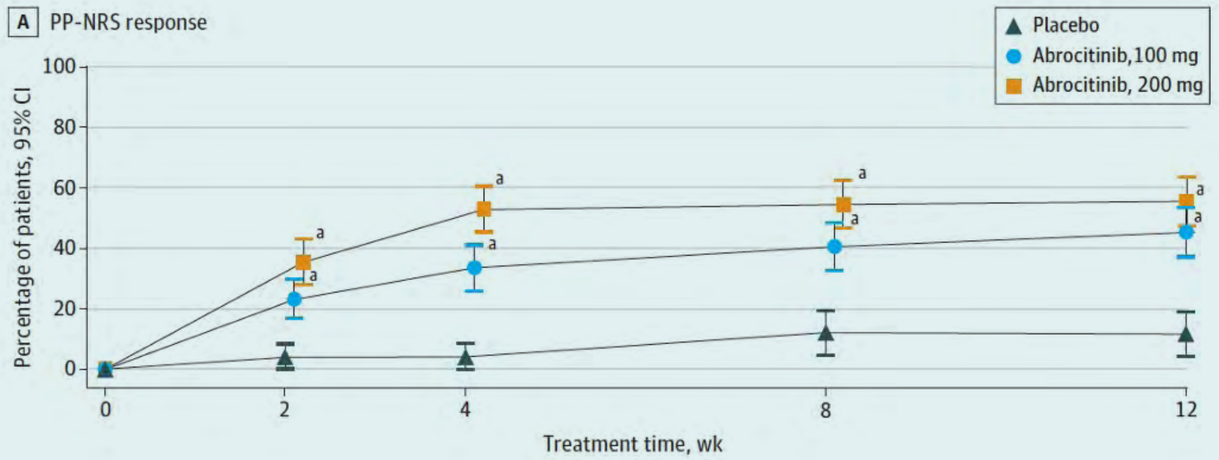
ABROCITINIB: PHASE 3 DATA

- Abrocitinib is an oral (QD), JAK1 inhibitor
- Phase 3 trial in patients 12 years or older with moderate-to-severe AD
- Approved for AD treatment as of 1/14/2022

Percentage of patients achieving IGA 0 (clear) or 1 (almost clear) and improvement of ≥2 points from baseline

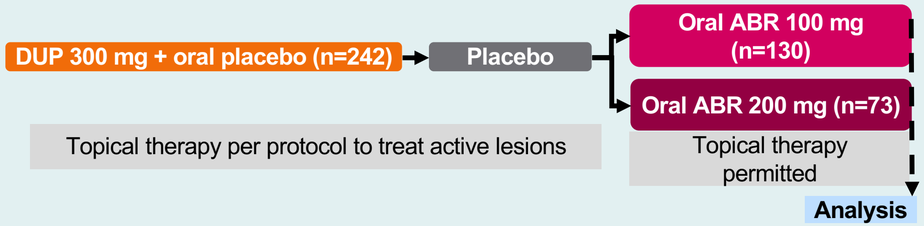


Percentage of patients experiencing ≥4 point improvement in peak pruritus from baseline



ABROCITINIB IN PATIENTS NOT ACHIEVING RESPONSES TO DUPILUMAB: JADE EXTEND

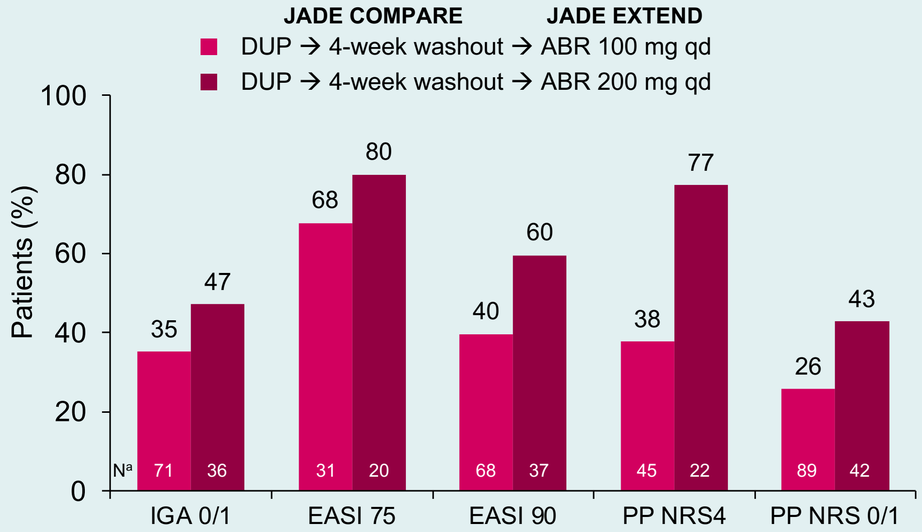
Study design



SAFETY

- Dose dependent increases in nasopharyngitis, nausea, acne, headache after switching to abrocitinib

Outcomes with abrocitinib at Week 12 of JADE EXTEND among nonrespondersa to 16 weeks' dupilumab in JADE COMPARE



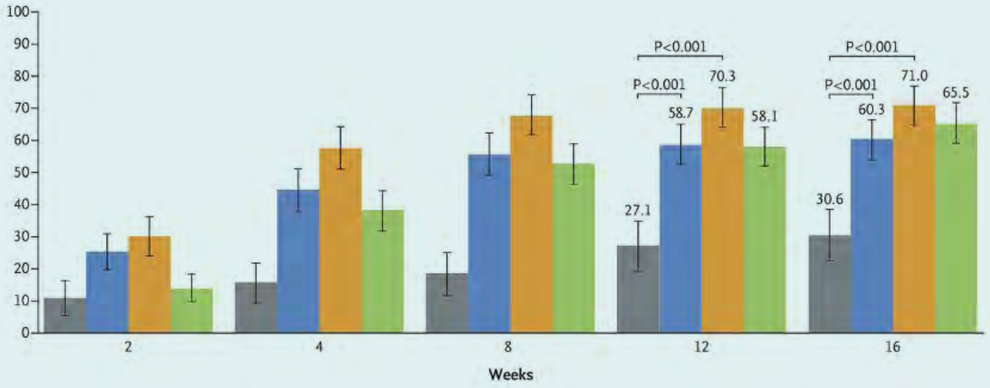
aNonresponders = patients receiving dupilumab who did not achieve the responses displayed at Week 16 of JADE COMPARE

Statistical methodology, including imputation methods, not included in poster

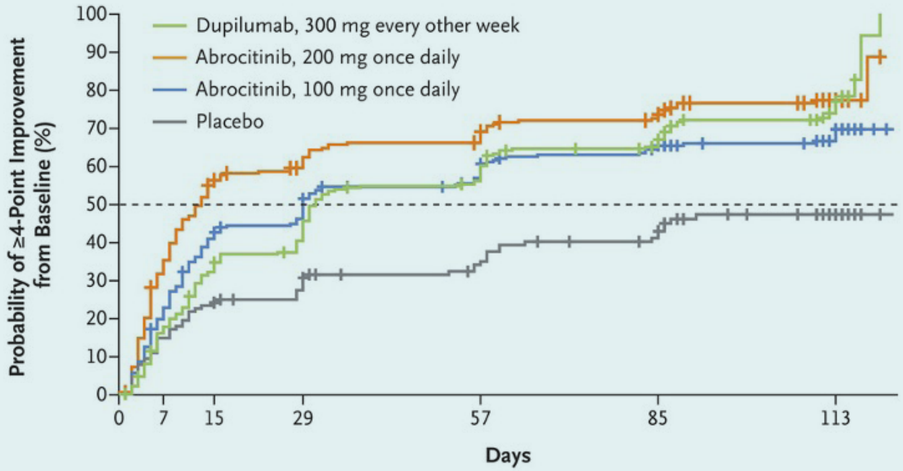
1. Bieber T, et al. N Engl J Med 2021;384:1101–12
Shi V, et al. AAD VMX 2021, P27590. Sponsored by Pfizer Inc.

ABROCITINIB VS PLACEBO OR DUPILUMAB: JADE COMPARE

- 16-week trial of abrocitinib 200 mg or 100 mg QD vs. dupilumab 300 mg Q2weeks* vs. placebo



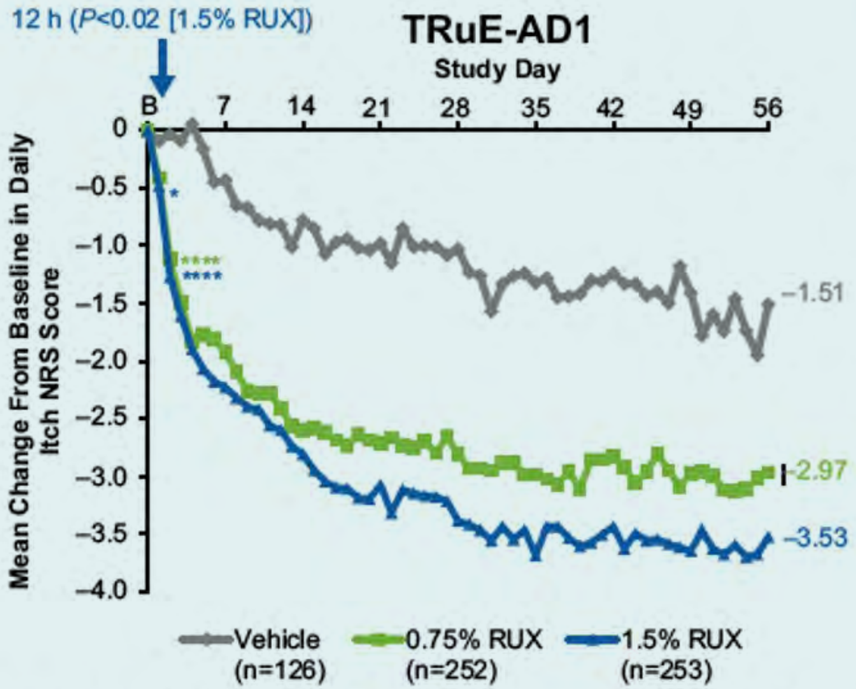
* After dupilumab 600 mg loading dose



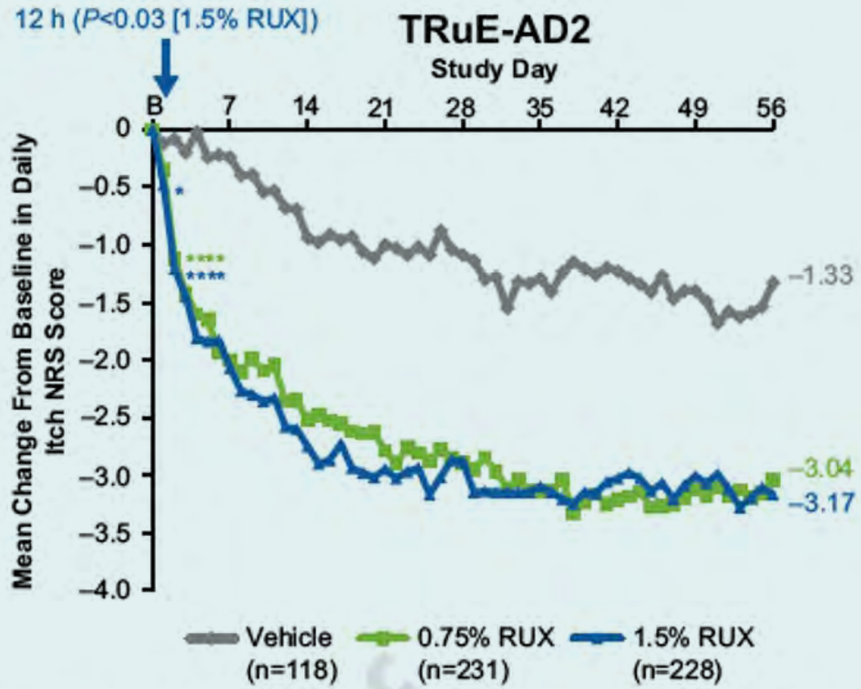
No. at Risk							
Dupilumab, 300 mg every other week	240	199	160	137	99	73	42
Abrocitinib, 200 mg once daily	226	153	100	86	70	53	24
Abrocitinib, 100 mg once daily	236	187	137	122	93	74	44
Placebo	130	110	99	89	76	65	29

Bieber T. et al. N Engl J Med 2021;384:1101-1112.

RUXOLITINIB 1.5% CREAM: PHASE 3 DATA



Number of Patients	Day 14	Day 28	Day 56
Vehicle	105	94	59
0.75% RUX	208	199	146
1.5% RUX	218	220	158

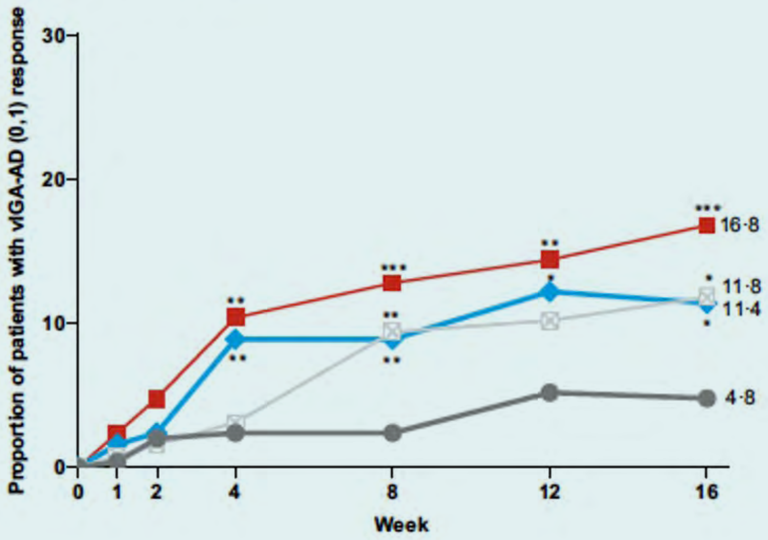


Number of Patients	Day 14	Day 28	Day 56
Vehicle	99	96	64
0.75% RUX	190	86	129
1.5% RUX	190	184	149

BARICITINIB: PHASE 3 DATA

- Baricitinib is an oral (QD), JAK1/2 inhibitor
- Two Phase 3 trials in patients 18 years or older with moderate-to-severe AD

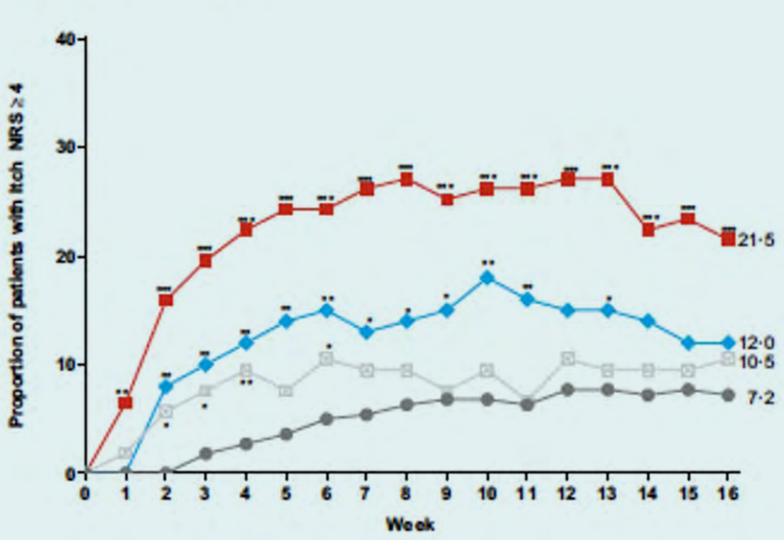
(a) Monotherapy[a]



BREEZE-AD1

Percentage of patients achieving IGA 0 (clear) or 1 (almost clear) and improvement of ≥2 points from baseline

(c) Monotherapy[a]

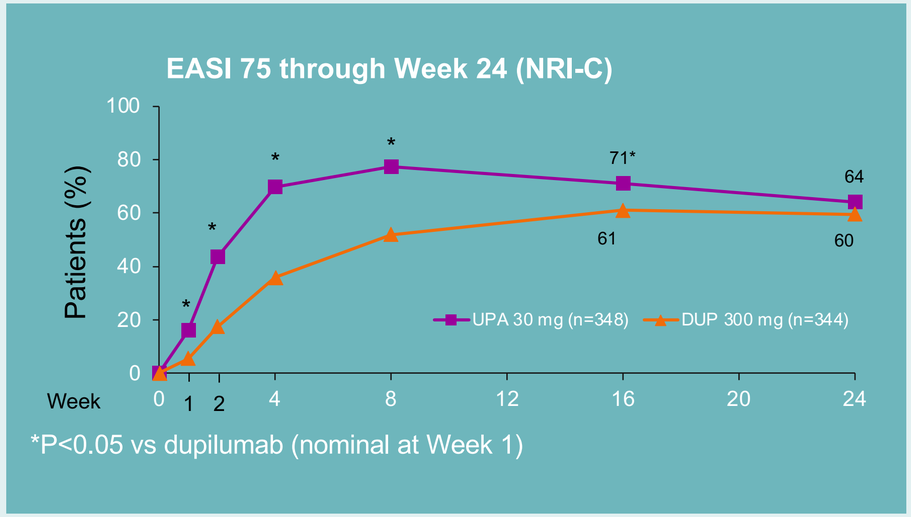


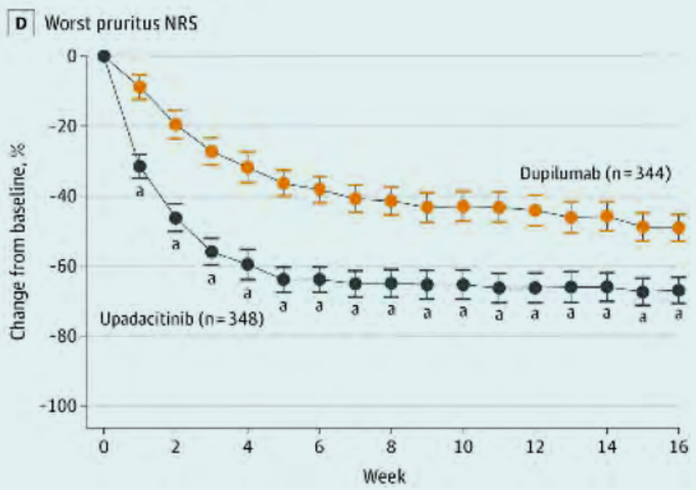
BREEZE-AD1

Percentage of patients experiencing ≥4 point improvement in peak pruritus from baseline

UPADACITINIB VS DUPILUMAB: HEADS UP

- 24-week trial of upadacitinib 30 mg QD vs. dupilumab 300 mg Q2weeks* in adults





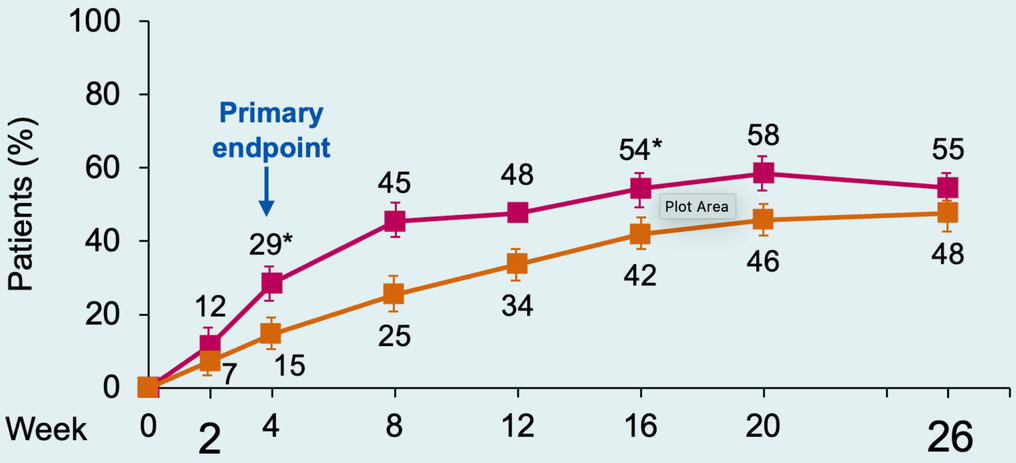
* After dupilumab 600 mg loading dose

Blauvelt A, et al. JAMA Dermatol 2021;157:1047-55.

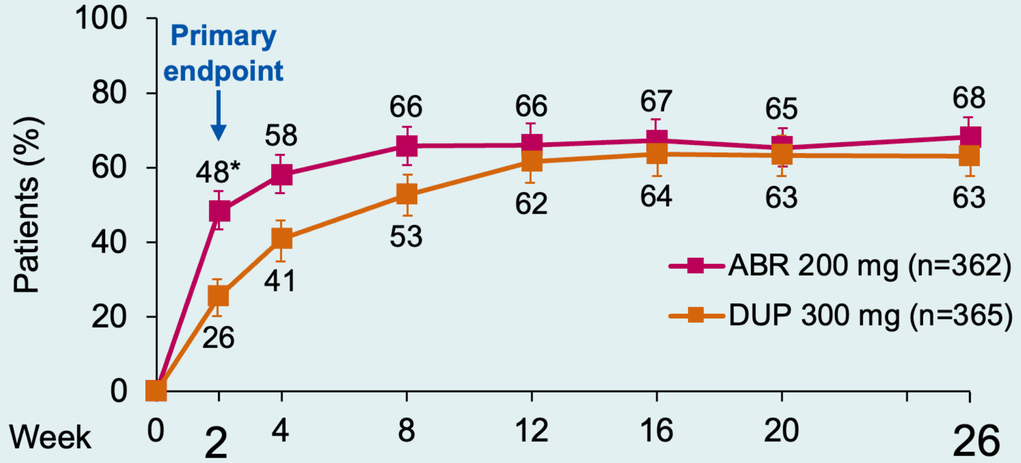
ABROCITINIB VS DUPILUMAB: JADE DARE

- 26-week trial of abrocitinib 200 mg vs. dupilumab 300 mg Q2weeks*

EASI 90 through Week 26 (NRI[a])



PP NRS through Week 26 (NRI[a])



*P<0.001 abrocitinib vs dupilumab; aPatients discontinuing treatment were imputed with NRI, for intermittent missing data no imputation was used
Reich K, et al. EADV 2021, late-breaking news D3T01.2B. Sponsored by Pfizer Inc.

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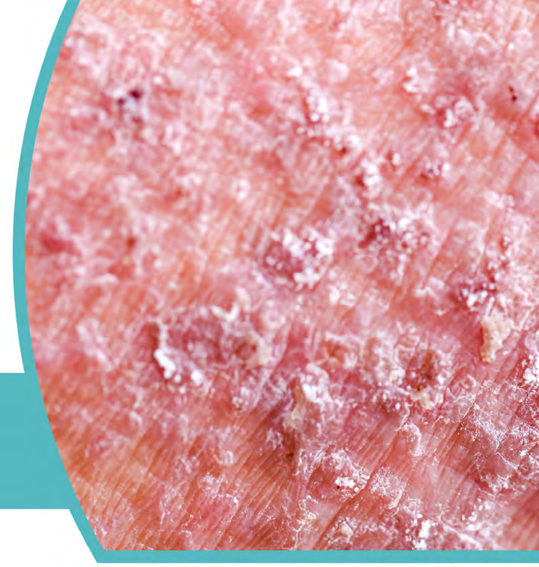


AD AND VACCINATION

Vaccination Guidelines for Patients With Immune-Mediated Disorders on Immunosuppressive Therapies

Kim A. Papp[1,2], Boulos Haraoui[3], Deepali Kumar[4,5], John K. Marshall[6], Robert Bissonnette[7], Alain Bitton[8], Brian Bressler[9,10], Melinda Gooderham[2,11], Vincent Ho[9], Shahin Jamal[12], Janet E. Pope[13,14], A. Hillary Steinhart[5,15], Donald C. Vinh[8,16], and John Wade[9,17]

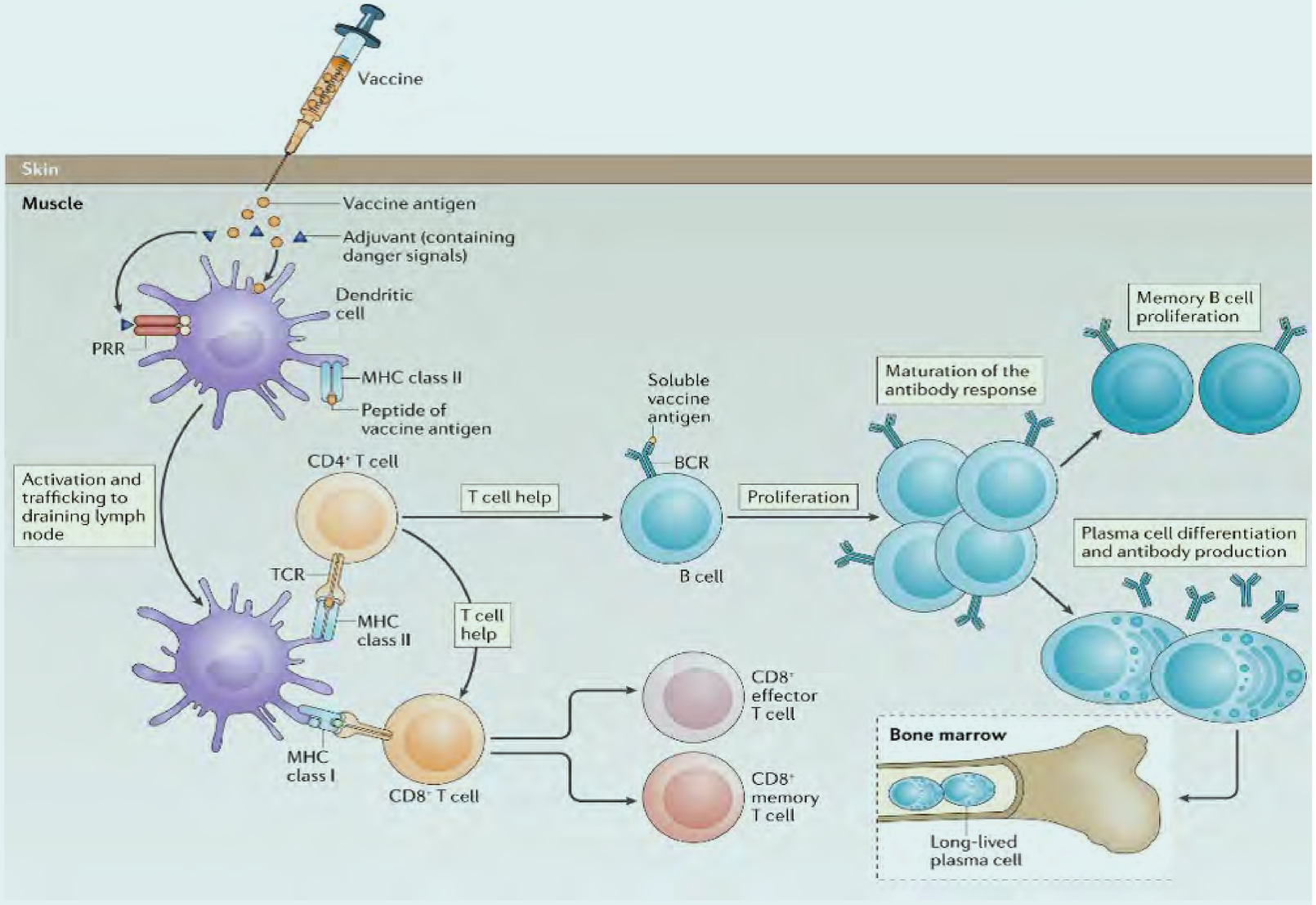
Journal of Cutaneous Medicine and Surgery
2019, Vol. 23(1) 50–74

DOI: 10.1177/1203475418811335
journals.sagepub.com/home/jcms
Canadian Dermatology Association
Association canadienne de dermatologie
CME

Update vaccination status according to local standards

Live-attenuate vaccines are unlikely to pose a significant threat

VACCINOLOGY HOW THEY WORK



Pollard AJ, Bijker EM. Nat Rev Immunol. 2021

The effect of tofacitinib on pneumococcal and influenza vaccine responses in rheumatoid arthritis

23-valent pneumococcal polysaccharide vaccine (PPSV-23)
2011–2012 trivalent influenza vaccine
25% on prednisone (unknown mean dose)
60% on MTX (unknown mean dose)

A (N=200)
randomised to tofacitinib 10 mg twice daily or placebo stratified by background methotrexate and vaccinated 4 weeks later

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Pneumococcal satisfactory response: tofacitinib 45.1%
placebo 68.4%

Satisfactory influenza responses: tofacitinib 56.9%
placebo 62.2%

Protective influenza titres (≥1:40 in two or more of three antigens): tofacitinib 76.5%
placebo 91.8%

Winthrop KL, et al. Ann Rheum Dis. 2016

The effect of tofacitinib on pneumococcal and influenza vaccine responses in rheumatoid arthritis

23-valent pneumococcal polysaccharide vaccine (PPSV-23)
2011–2012 trivalent influenza vaccine.

B (N=183)
patients already receiving tofacitinib 10 mg twice daily (with or without methotrexate) randomised

those continuing ('continuous') or
interrupting ('withdrawn') tofacitinib for 2 weeks

vaccinated 1 week after

PPSV-23 : 75.0% - continuous and 84.6% - withdrawal

influenza : 66.3% - continuous and 63.7% - withdrawal

Winthrop KL, et al. Ann Rheum Dis. 2016

T-cell-mediated immune response to pneumococcal conjugate vaccine (PCV-13) and tetanus toxoid vaccine in patients with moderate-to-severe psoriasis during tofacitinib treatment
Winthrop KL, et al. JAAD 2018

Most psoriasis patients who receive tofacitinib can mount satisfactory T-cell-dependent responses to PCV-13 and tetanus vaccines

---

Evaluation of pneumococcal and tetanus vaccine responses in patients with rheumatoid arthritis receiving baricitinib: results from a long-term extension trial substudy
Winthrop KL et al. Arth Res Ther 2019

Two thirds of patients on long-term baricitinib achieved satisfactory humoral and functional responses to PCV-13 vaccination
TTV responses were less robust
PCV-13 response was not diminished in those taking concomitant corticosteroids

Zoster

Indicated for age 50+
Administered as two doses 2 – 6 (12) months apart
90% (85 – 95) reduction of zoster for at least 4 years
90% (69 – 97) reduction in PHN
Effectiveness consistent across all age groups

Increased risk of Guillain-Barre syndrome within 42 days of vaccination
RR 4.96 (1.43 – 17.27) in 849,397 RZ

Cunningham Al et al NEJM 2016
Cunningham AL, et al. J Infec Dis 2018
Goud R, et al. JAMA Internal Medicine 2021
https://www.fda.gov/media/108597 (package insert)

Safety

- Contraindications regarding the use of live vaccines:
  - few data support extraordinary safety for expectant doses of immunosuppressants.
- Risk of acquiring significant infection with live vaccines
  - increased with broad immunosuppression or specific T-cell dysfunction.
- There is a small risk of brief, moderate exacerbation of the underlying disease as a result of general immune activation following vaccination.