

MTA
Kiváló Kutatóhely



How to use JAK inhibitors?

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Euroderm Excellence
Budapest, 12 November 2024.

Immune-mediated inflammatory skin diseases significantly impact patients' quality of life



Psoriasis



Atopic
dermatitis



Alopecia
areata



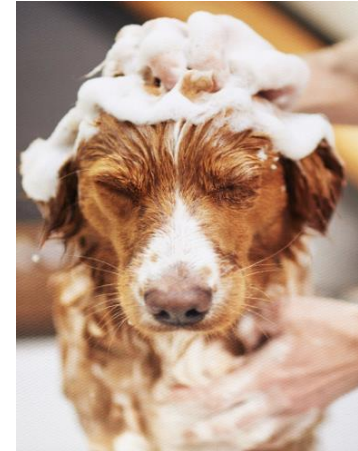
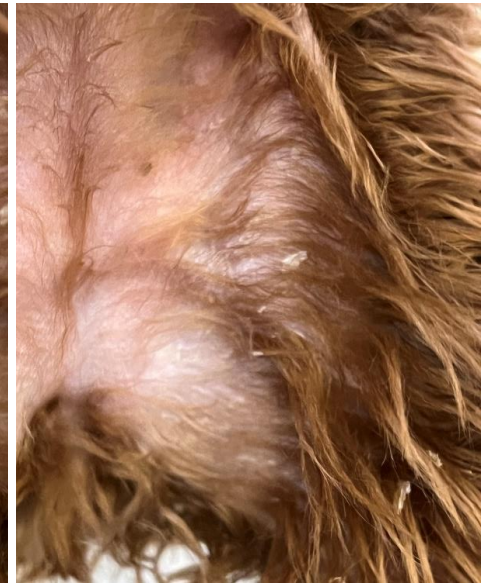
Hidradenitis
suppurativa

Immune-mediated inflammatory skin diseases significantly impact the canine's quality of life



12 months old, female

Provoking factors



Stress/allergy?

Irritants?

Severe canine atopic dermatitis

2-years old female
6-month history of atopic dermatitis

Previous treatments:

- 0.5 mg/kg prednisolon
- 4 mg/kg cyclosporin



0.5 mg/kg oclacitinib (JAK1 inhibitor)



Complete clearing of the lesions



1

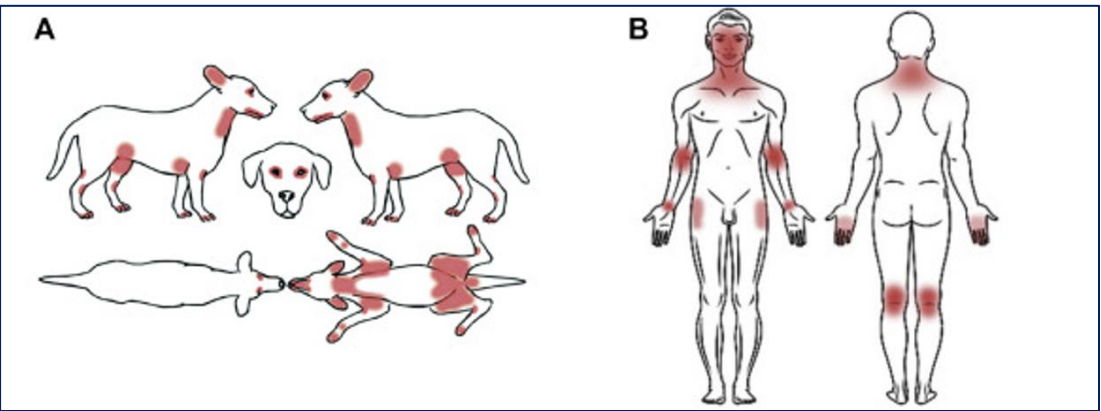
Before



2

2 month after

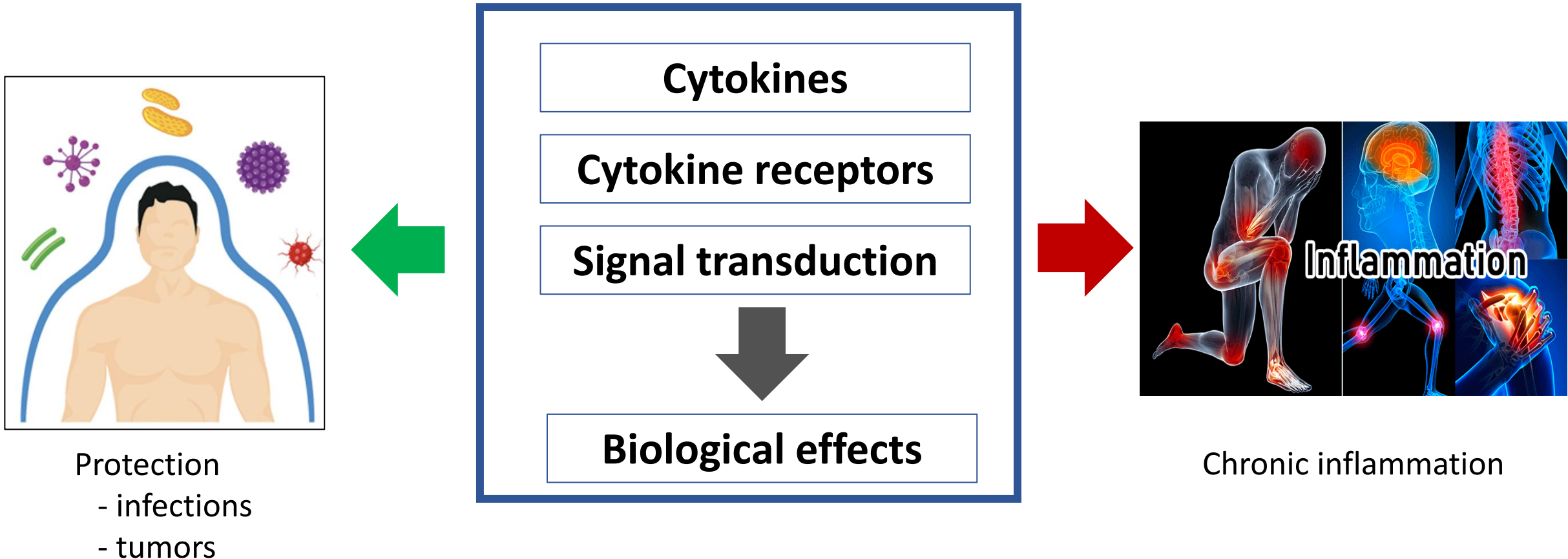
Canine atopic dermatitis



Treatment:

- JAK1 inhibitor (oclacitinib)
- anti-IL-31 monoclonal antibody (lokivetmab)

Targets in immun-mediated inflammatory skin diseases



Weapons: monoclonal antibodies, small molecules

Content

Mechanism of action of JAK inhibitors

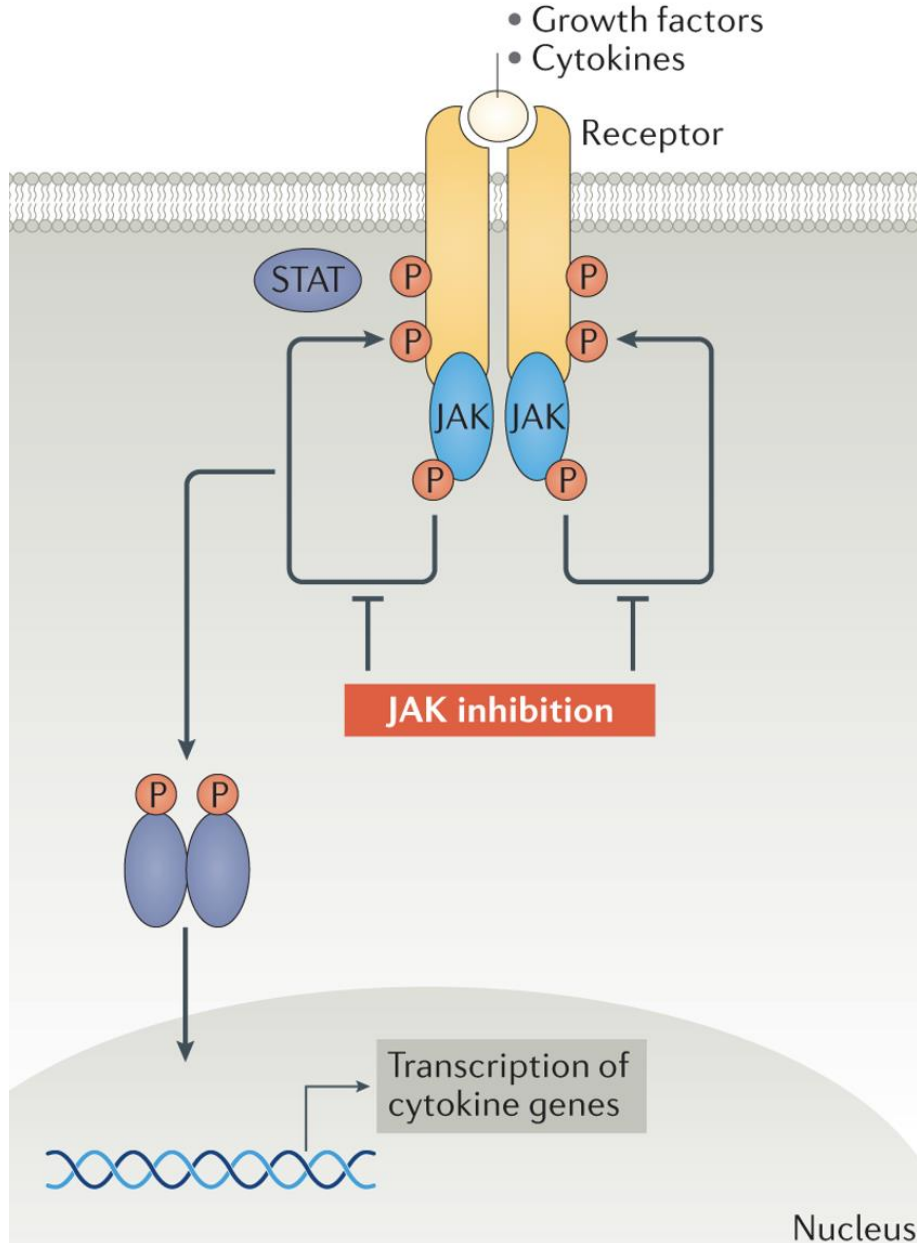
Efficacy and safety issues

Approved indications

Case reports

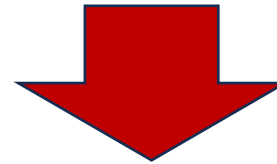
Expanding indications

Mechanism of action of Janus kinases (JAKs)

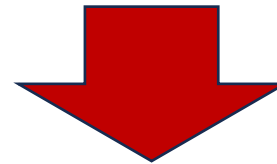


4 JAK isoforms:

JAK1, JAK2, JAK2, Tyrosine kinase 2 (TYK2)

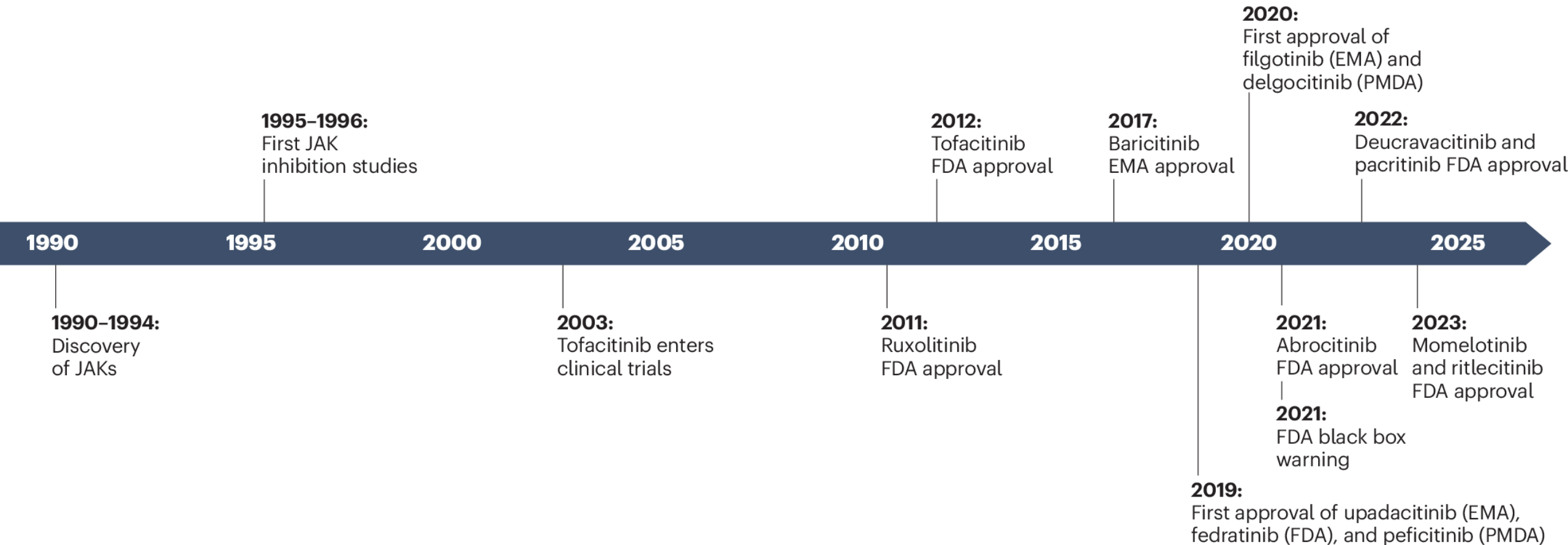


7 STAT transcription factors

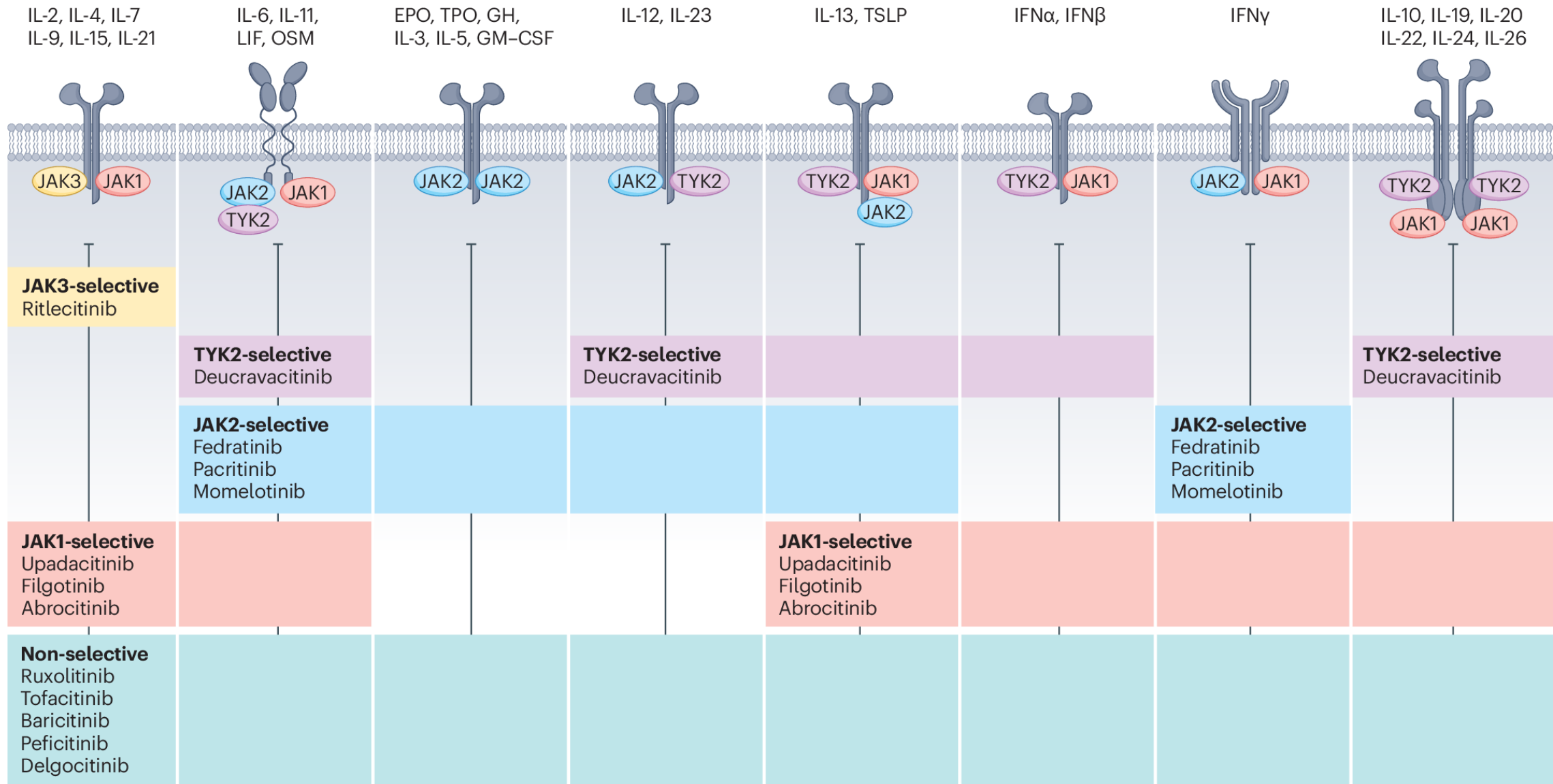


Biological effects

Timeline of JAK inhibitor development



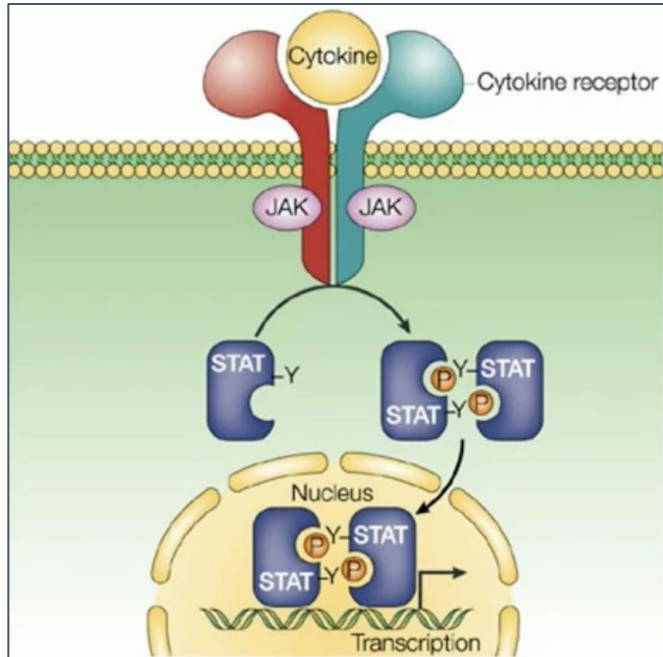
JAKs are pivotal in mediating the signaling of various cytokines and hormones



Selectivity of JAK inhibitors

Predicting the effects of cytokine signaling based on JAK selectivity is challenging.

- JAKs functions in pairs
- Functional role for a given JAK isoform varies between cytokine receptors
- Difficulties measuring the selectivity



Selectivity measurements

- Biochemical activity-based assessment
- Biochemical binding-based assessment
- Cell-based assessment

Efficacy of JAK inhibitors

- In theory, selective JAK inhibitors should be more targeted treating a given IMiD with fewer side effects
- The in vitro studies for selectivity, that may not represent in vivo studies
- Efficacy depends on a given IMiD, differential JAK expression in the tissues
- Individual SNPs in STAT isoforms among patients



If a patient does not respond to a given JAKi, might respond to another one!

Adverse reactions of JAK inhibitors in AD

Abrocitinib ^{1*,a, b}	Baricitinib ^{2**, b}	Upadacitinib ^{3***, b}
<ul style="list-style-type: none"> Nausea 	<ul style="list-style-type: none"> Hypercholesterolemia Upper respiratory tract infections 	<ul style="list-style-type: none"> Acne Upper respiratory tract infections
<ul style="list-style-type: none"> Abdominal pain upper CPK increased > 5 x ULN Headache Herpes simplex 	<ul style="list-style-type: none"> Abdominal pain CPK increased > 5 x ULN Headache Herpes simplex 	<ul style="list-style-type: none"> Abdominal pain Blood CPK increased Headache Herpes simplex
<ul style="list-style-type: none"> Acne Herpes zoster 	<ul style="list-style-type: none"> Acne Herpes zoster Rash Urinary tract infection 	<ul style="list-style-type: none"> Herpes zoster Rash Urinary tract infection
<ul style="list-style-type: none"> Dizziness Vomiting 	<ul style="list-style-type: none"> Gastroenteritis Pneumonia Folliculitis Thrombocytosis > 600 x 10⁹ cells/L 	<ul style="list-style-type: none"> Anemia Fatigue Folliculitis Bronchitis ALT increased AST increased Influenza Nausea Neutropenia Lymphopenia NMSC Hypercholesterolemia Pyrexia Urticaria Weight increased Hyperlipidemia

CK elevation: not worrying lab abnormality!

Prevention and management dermatological side effects

Zoster prevention:

Vaccinate your patient with Shingrix vaccine

Varivax (varicella vaccine) is not a good option

JAK-acne:

Conventional treatment, but based on the severity of acne and AD, you may consider to reduce the does of a given JAKi

EMA recommendation to risk minimization for JAK inhibitors

JAK inhibitors should be used only if no suitable treatment alternatives are available in patients:

- aged 65 years or above
- at increased risk of MACE (major adverse cardiac event)
- those who smoke or have done so for a long time in the past
- those at increased risk of cancer

JAK inhibitors should be used with caution in patients with:

- risk factors for blood clots in the lungs and in deep veins (venous thromboembolism, VTE) other than those listed above.

Wollenberg et al: Absolute risk of additional MACE, VTE or cancer events with JAKi, extrapolated from comparison with TNFi in patients with RA, appears to be low.

Approved indications

Psoriasis

Plaque type



inverse



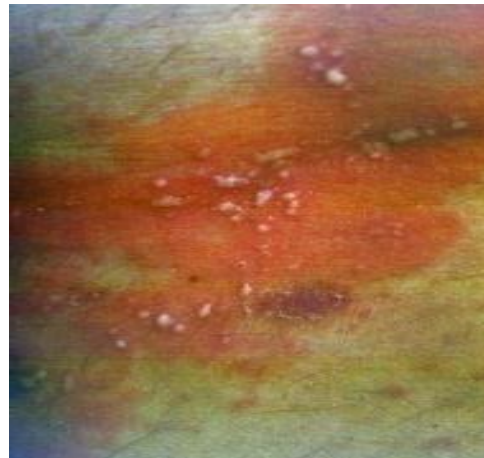
Pustular



Guttate



Erythrodermic



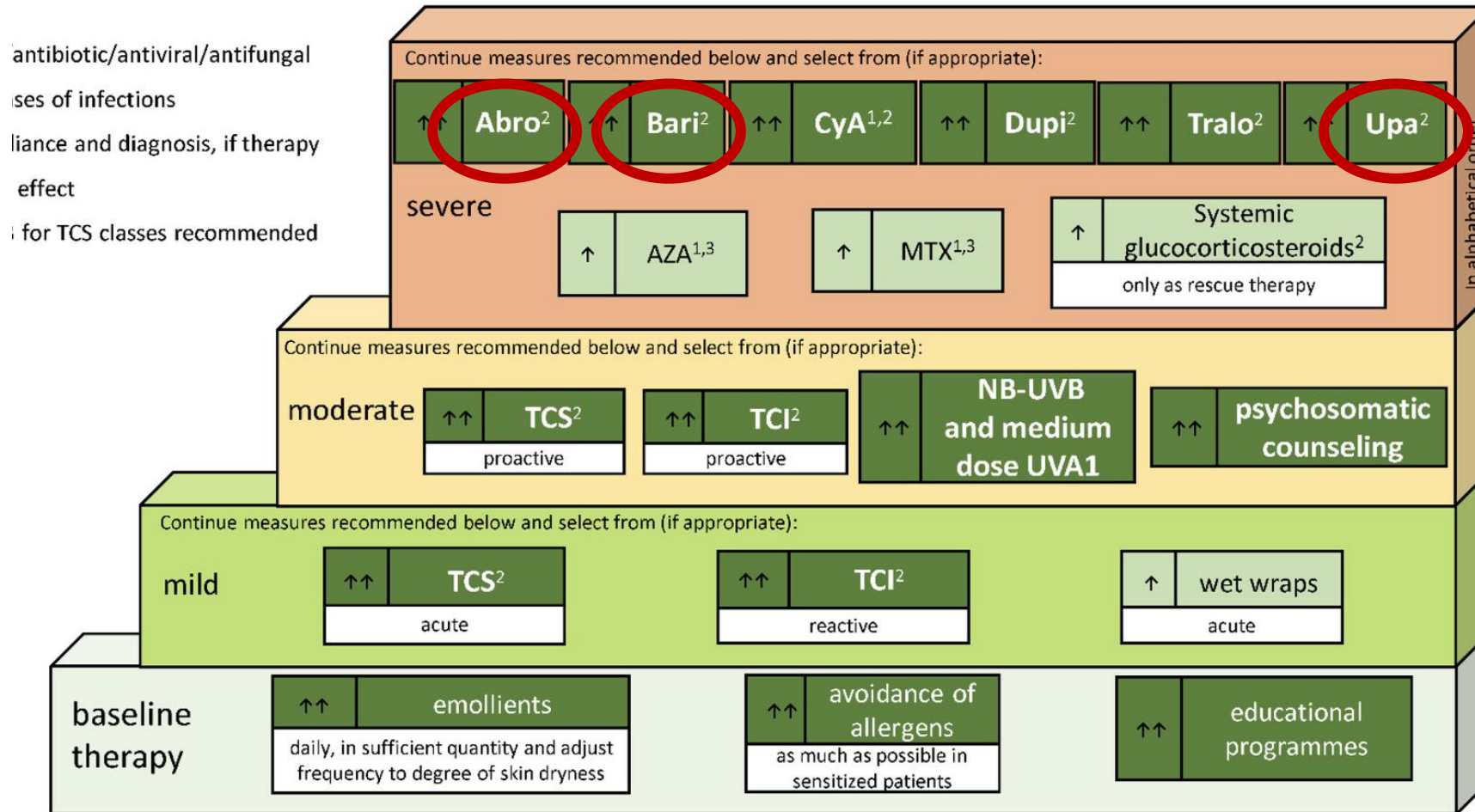
JAK inhibitors?

JAK inhibitors in psoriasis and in psoriatic arthritis

- Non-selective tofacitinib approval in PsA in 2017, efficacy confirmed in PSO, but not approved in PSO.
- JAK1 selective upadacitinib approval in PSA 2021.
- TYK2 selective deucravacitinib approval in PSO in 2022/2023.

JAK inhibitors for atopic dermatitis

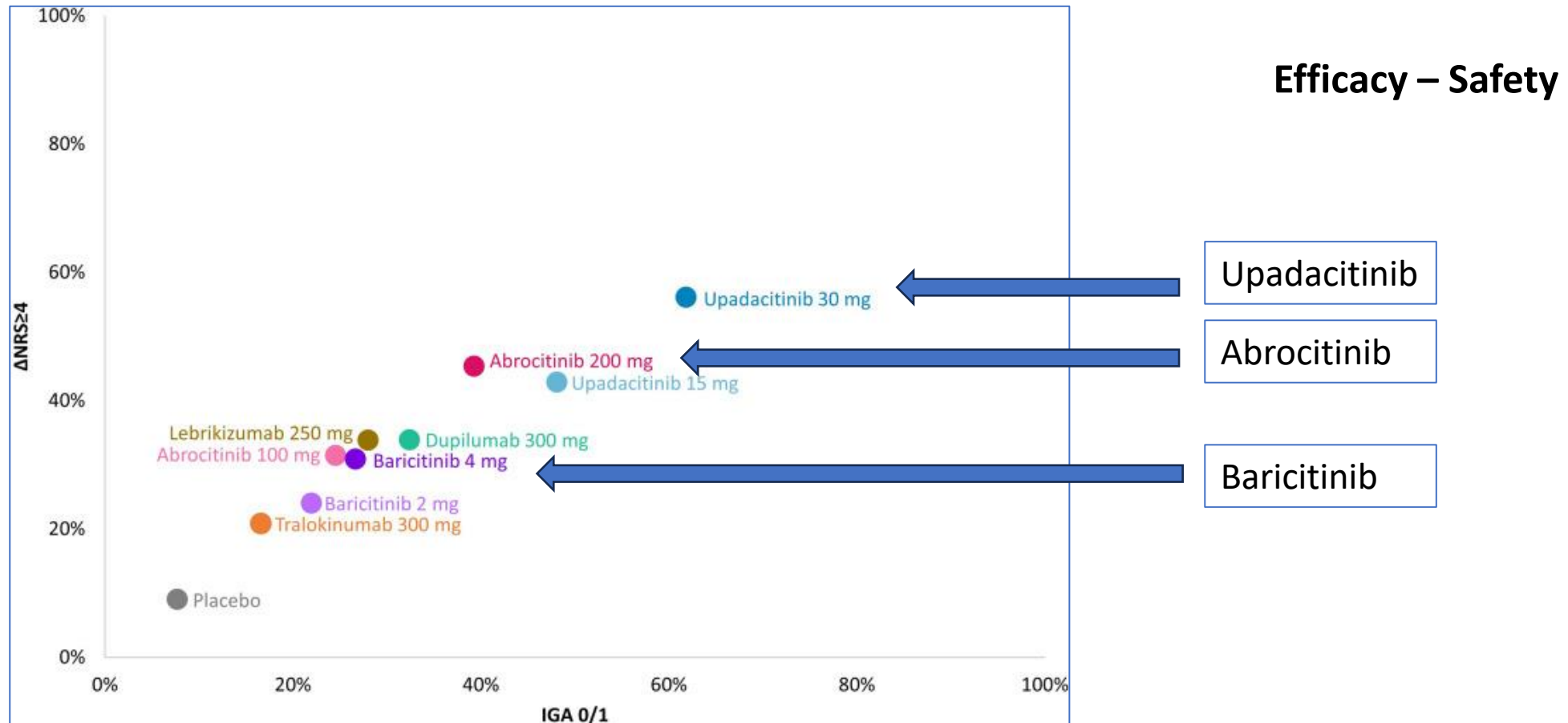
European Guideline



Baricitinib JAK1/2 i
 Upadacitinib JAK1 i
 Abrocitinib JAK1 i

Which one to choose?

Network Meta-analysis: 13 unique placebo-controlled trials involving 7105 patients





Systemic Treatments for Atopic Dermatitis (Eczema)

Systematic Review and Network Meta-Analysis



149
RCTs



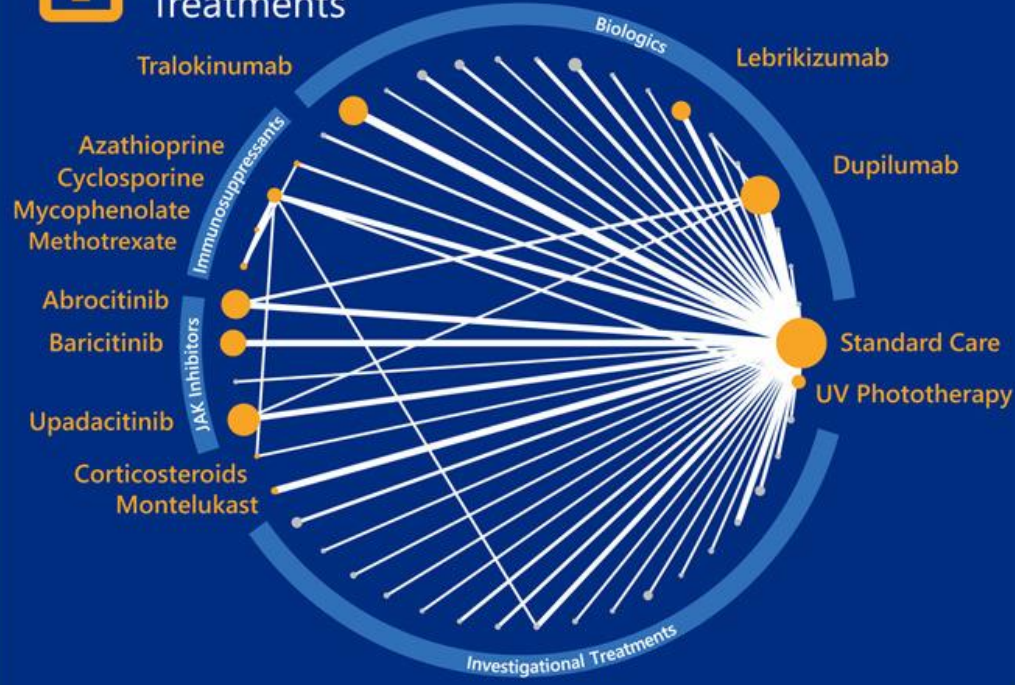
28 686
Participants

Age Groups
Pediatric + Adult

Eczema Severity
Moderate-to-Severe



75
Treatments



Disease Activity



Itch Severity



Sleep Disturbance



Quality of Life



Eczema Flares



Adverse Events

GRADE

Summary Table

Decision-Making Aid

Treatments	Outcomes			
	1	2	3	4
	Green	Green	Green	Red
	Green	Green	Green	Red
	Green	Green	Green	Red
	Green	Green	Green	Red
	Green	Green	Green	Red

Conclusions

High-dose upadacitinib was among the most effective for multiple outcomes, but also among the most harmful

Dupilumab, lebrikizumab, and tralokinumab are generally of intermediate effectiveness and favourable safety

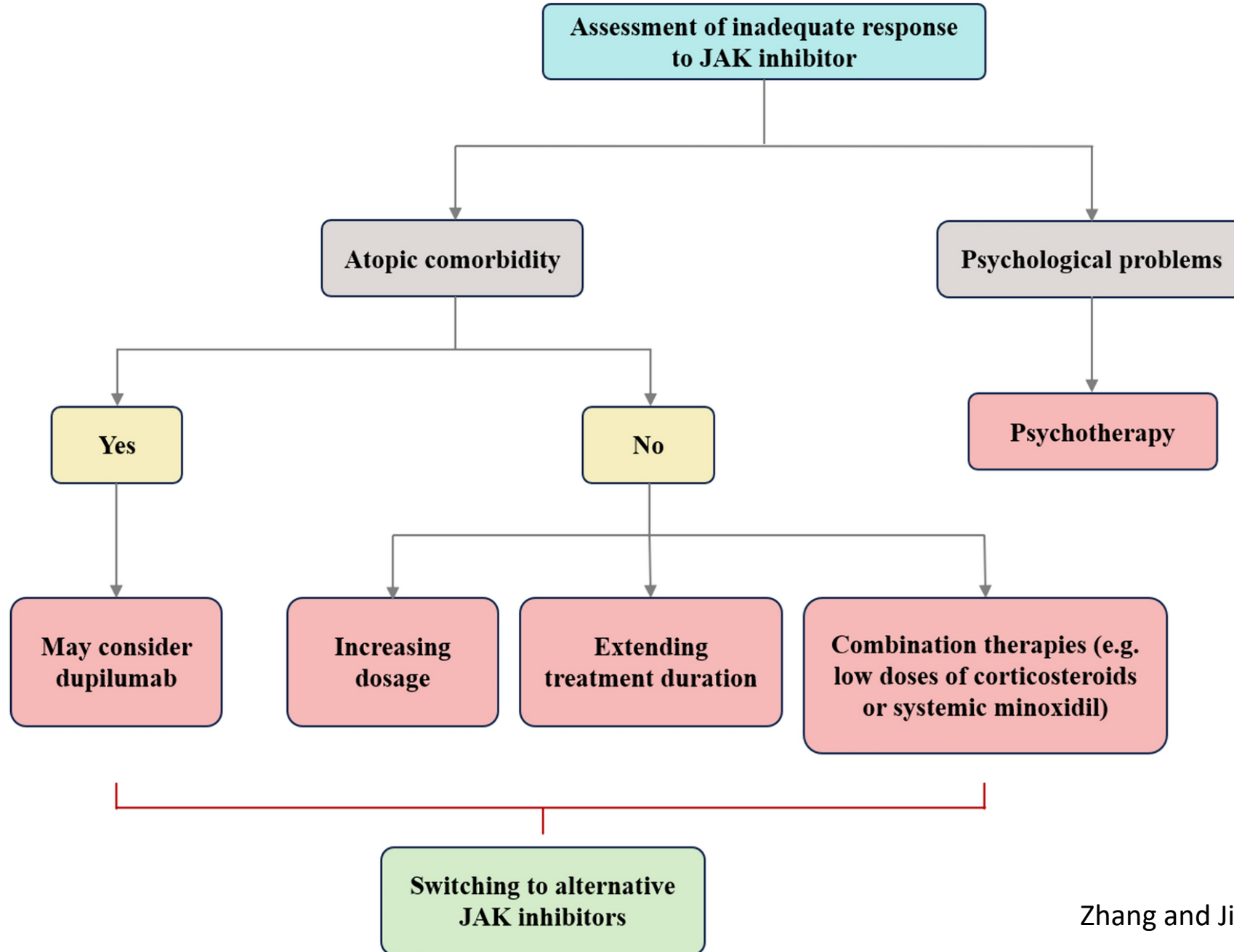


Alopecia areata



Baricitinib: JAK1/2i - approved by FDA/EMA in 2022 above 18 year
Ritlecitinib: JAK3i - approved by FDA/EMA in 2023 above 12 year
Deuruxolitinib: JAK1/2i - expected approval in 2025

Management of an inadequate response to JAK inhibitors in patients with AA



Alopecia areata with Atopic dermatitis

Efficacy of Dupilumab



Increased IgE is a good marker for the good therapeutical efficacy.

RESEARCH SUMMARY

Two Phase 3, Randomized, Controlled Trials of Ruxolitinib Cream for Vitiligo

Rosmarin D et al. DOI: 10.1056/NEJMoa2118828

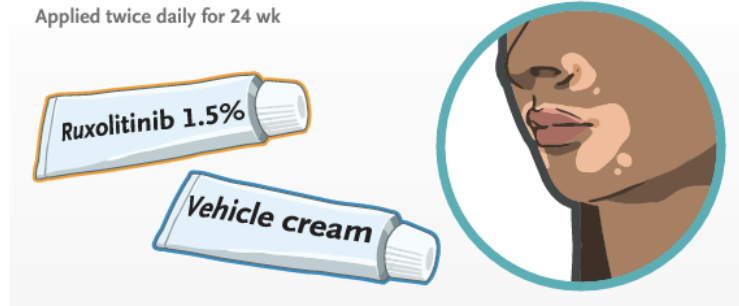
CLINICAL PROBLEM

As of June 2022, there were no approved treatments for repigmentation of vitiligo lesions in the United States or Europe. Ruxolitinib, an inhibitor of Janus kinase 1 and 2, showed promise in a phase 2 trial, but additional data are needed.

CLINICAL TRIALS

Design: Two phase 3, double-blind, randomized, vehicle-controlled trials examined the efficacy of ruxolitinib cream for repigmentation of skin lesions in adolescents and adults with nonsegmental vitiligo.

Applied twice daily for 24 wk



Vitiligo

Topical Ruxolitinib JAK1/2 i

Expanding indications

Clinical trials

AD, AA, HS, DM

Vitiligo, GVHD

Prurigo Nodularis

Chronic hand eczema

Sjögren sy

Case reports/case series

Palmoplantar pustulosis

BP, Pemphigus, LE, Morphea

Lichen planus, rosacea

Behcet, sarcoidosis, Darier

Hypereosinophil sy

Granuloma annulare

Sjögren sy

Case reports

Atopic dermatitis and spondylarthritis ankylopoetica

- 1998 atopic dermatitis (AD)
 - 2009 spondylarthritis ankylopoetica (SPA)
 - 2010 ADA for SPA
 - 2019 ADA plus cyclosporin
 - 2020: ADA plus dupilumab
- 2020-2021
- AD: highly improved
SPA: asymptomatic
- 2021
- Eyes: severe conjunctivitis,
Face: severe AD
SPA: asymptomatic (under adalimumab)



Dupilumab switch to baricitinib for AD and SPA

Tisztelt Professor Úr!



Örömmel értesítem hogy nagyon jól vagyok



Igazság szerint ez nekem az álom bőr kategória!!!

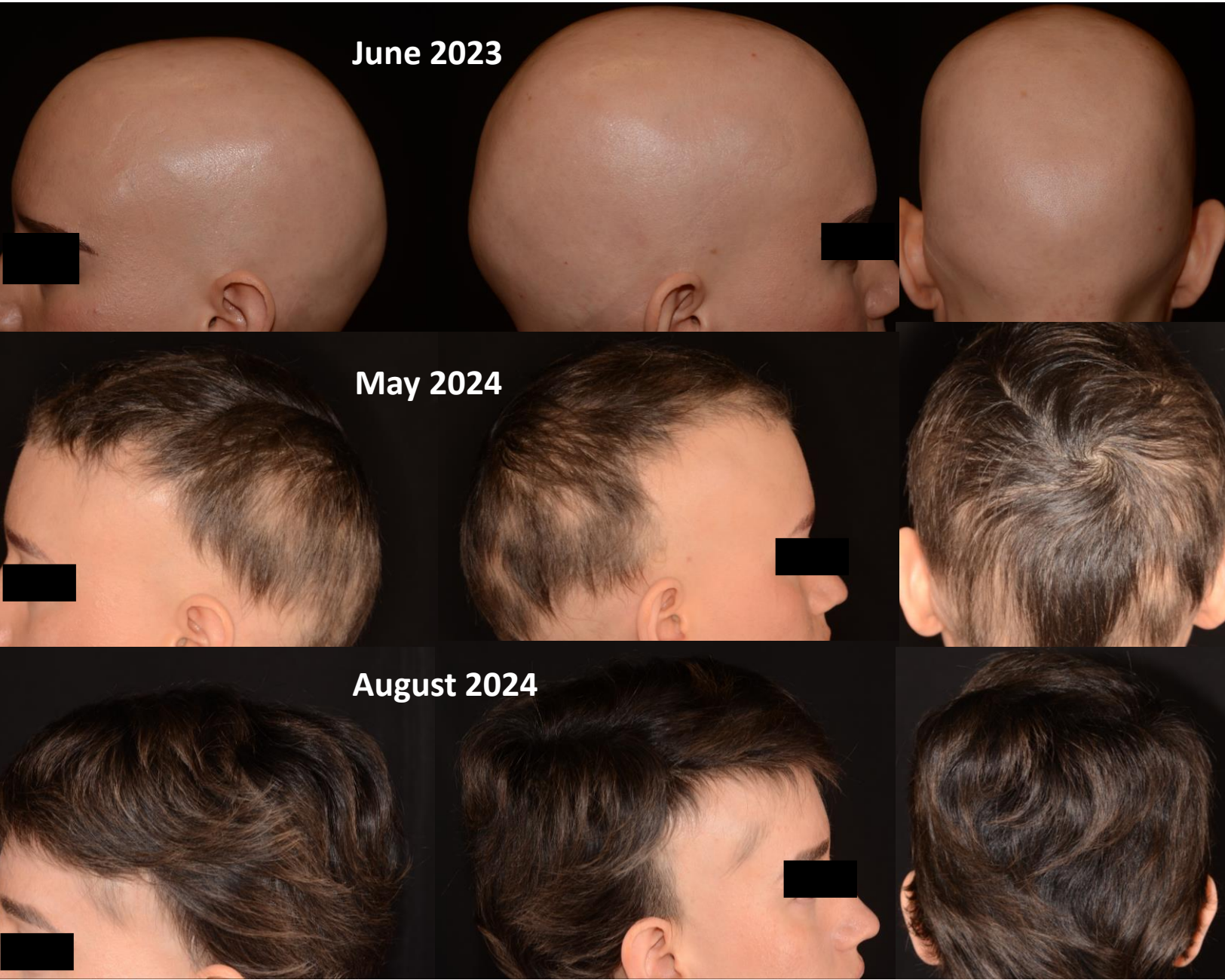
SPA:

Progression after stopping ADA



JAK inhibitor + adalimumab?

JAK inhibitor in alopecia areata



June 2023

May 2024

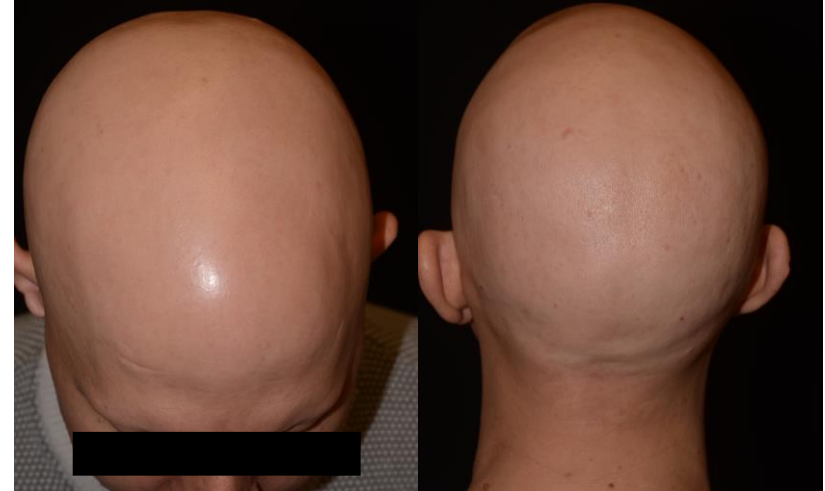
August 2024

30-year-old woman

- Nov 2022 spotted AA
- January 2023 AU
- **June 2023 Baricitinib**
- May 2024. No efficacy in occipital region, no regrowth of eyebrows, eyelashes
- + 1.25 mg minoxidil per dose per day

August 2024

- almost complete hair regrowth, except in the temporal region



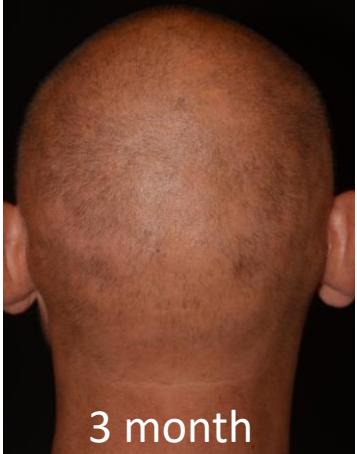
June 2023 JAK inhibitor launch

May 2024 only minimal hair growth in the beard area

+ 2.5 mg minoxidil per dose per day

August 2024 Approximately 80% hair regrowth (grade I CK elevation)





3 month



7 month



7 month



14 month

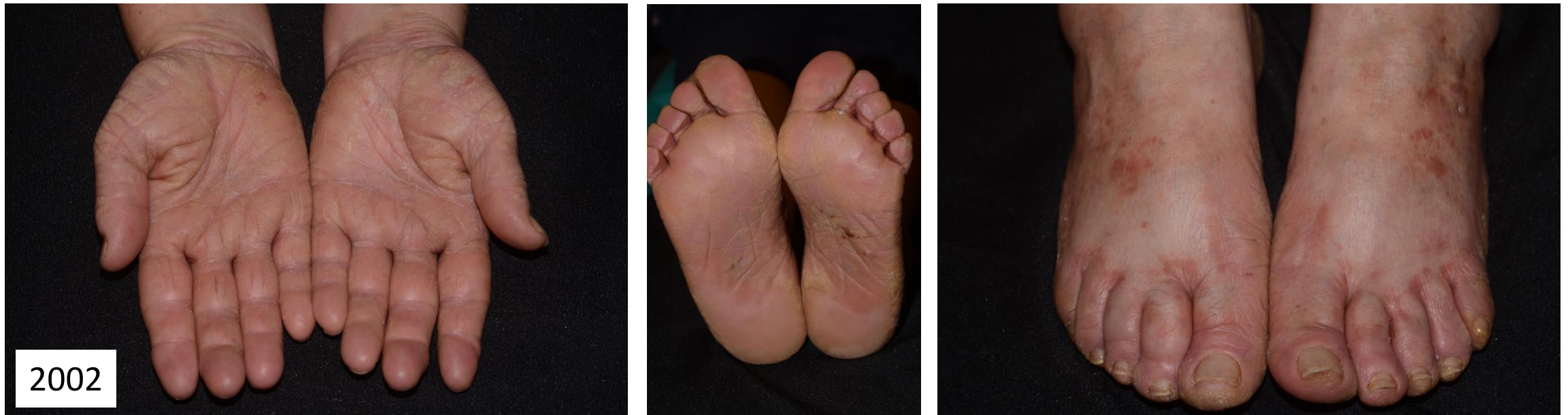
Psoriasis and Atopic dermatitis

46-yrs old female patient

Personal and family anamnesis: no PSO, AD, or other IMID

Skin disease started in 2002 mainly in palmoplantar localization

Therapy: PUVA – without significant improvement



2004: PsA – infliximab infusions, but after 3 infusions, this therapy was stopped

48 y/o female palmoplantar lesions



2004



The clinical spectrum of palmoplantar diseases





A histological section of skin stained with hematoxylin and eosin (H&E). The image shows the epidermis with a thickened stratum corneum at the top, characteristic of parakeratosis. Below this, the epidermal layers exhibit marked spongiosis, with numerous vesicles (spaces) between the keratinocytes, indicating an inflammatory process. The nuclei of the keratinocytes are stained dark purple, and the cytoplasm and extracellular matrix are stained pink.

parakeratosis

marked spongiosis
vesiculation



**48 y/o female palmoplantar
lesions**

Palmoplantar psoriasis



Plaques not exclusively on the palmoplantar area



Nail involvement

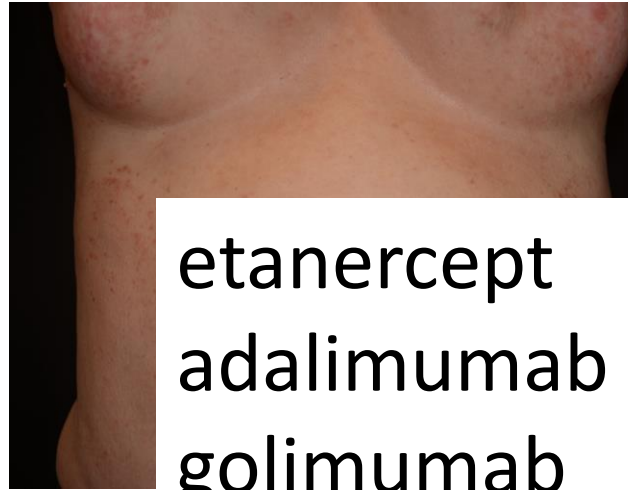


Minor improvement under acitretin therapy



2010-2011: MTX, CyA – tolerance issues, no improvement

Minor or no improvement under different treatments



etanercept
adalimumab
golimumab
ustekinumab
secukinumab
ixekizumab
guselkumab



2011-2022.



Upadacitinib therapy resulted a major improvement of the skin symptoms 2022-



The patient is satisfied with the results, with no side effects.

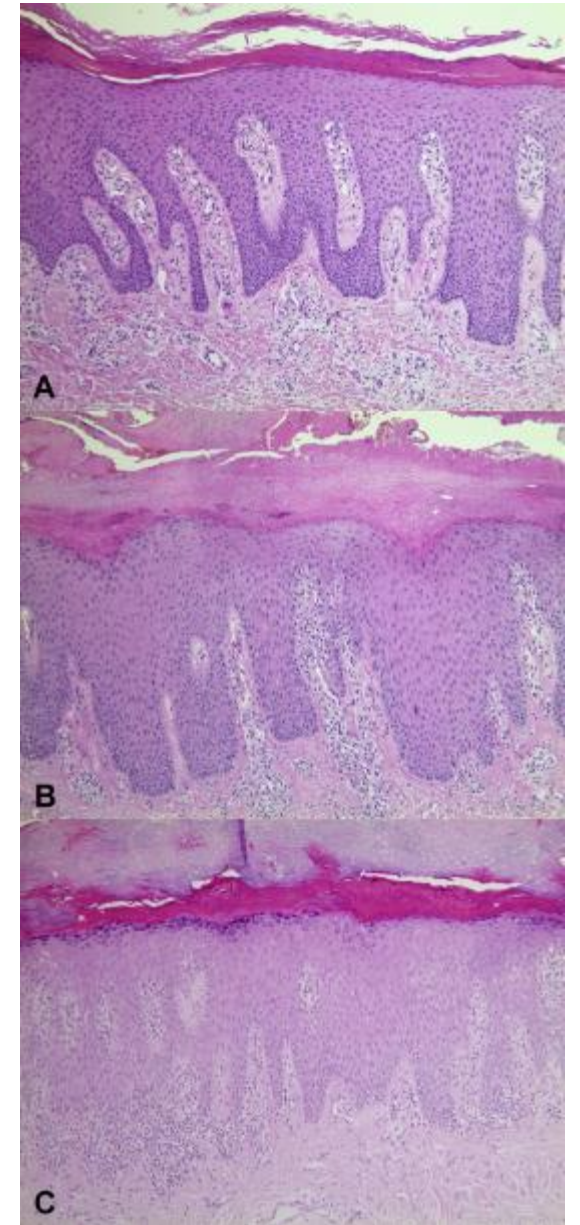
Clinical manifestations of hyperkeratotic palmar lesions



A
Psoriasis

B
hand eczema

C
hyperkeratotic
hand dermatitis



Discussion points

- Efficacy – safety
- Difficult to treat patients
- Combination therapies