CHARITÉ
UNIVERSITÄTSMEDIZIN BERLIN

Hair Disorders

Challenges and New Treatment Options for Dermatologists in Daily Practice

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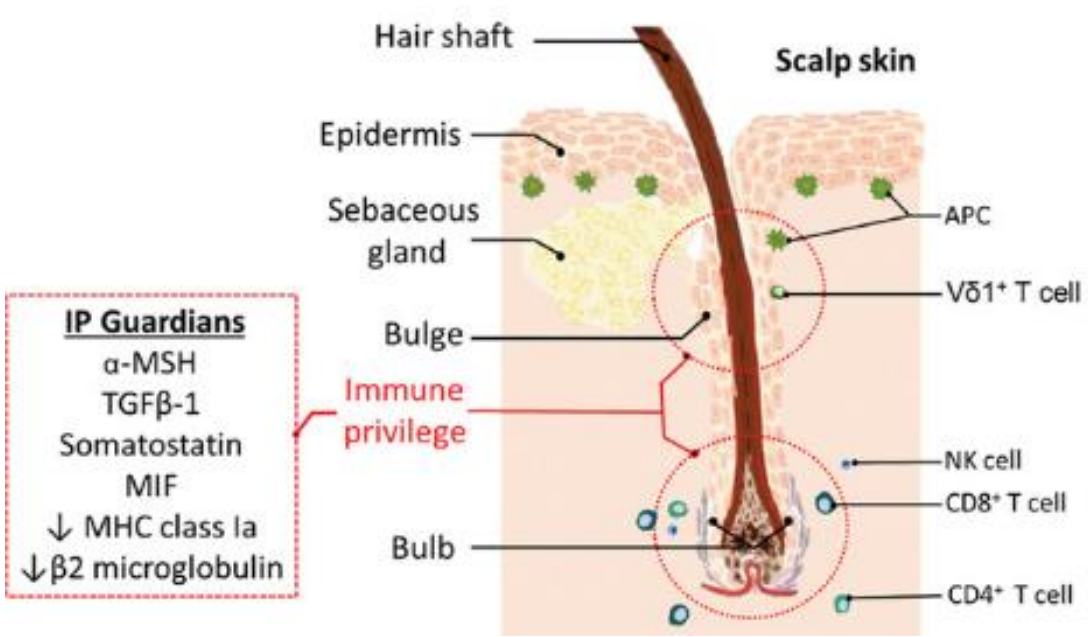
and Allergology

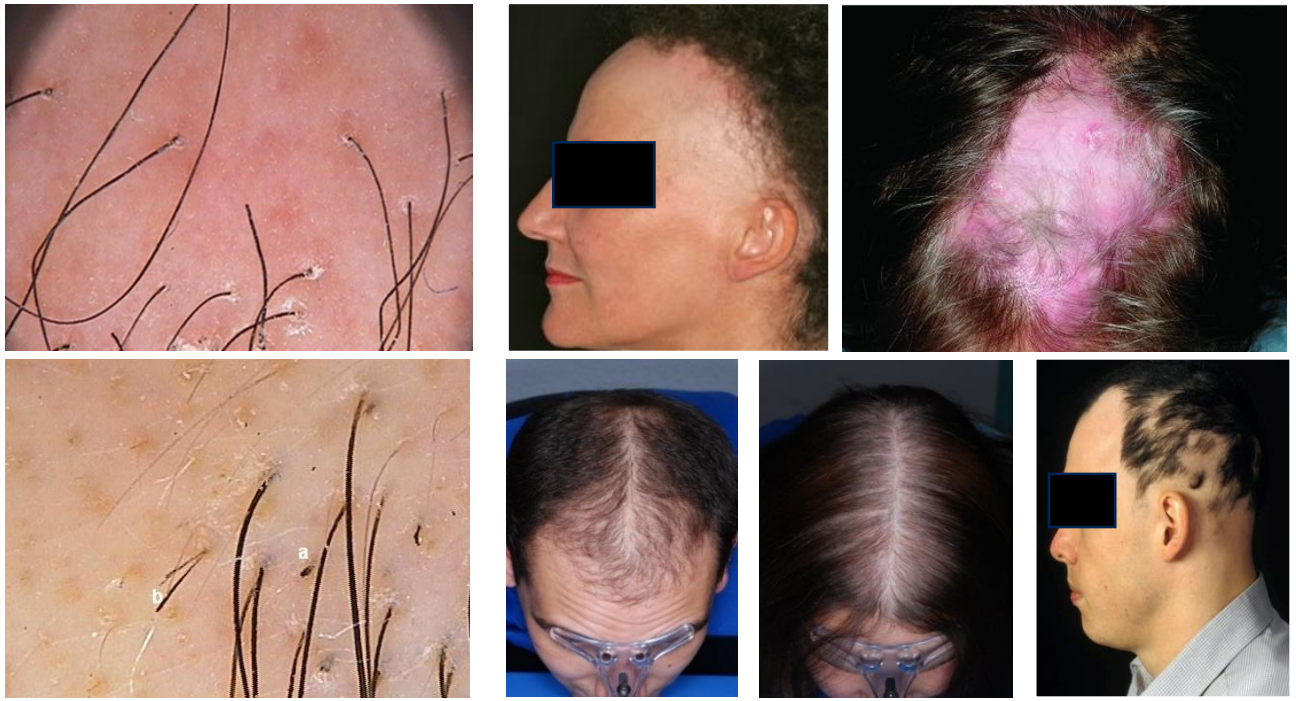
Conflict of Interest Declaration

Type of affiliation / financial interest	**Name of commercial company**
Receipt of grants/research supports:	Pfizer, Novartis, Concert/ Sun Pharma
Receipt of honoraria or consultation fees:	Abbvie, Boots Healthcare, Cantabria Labs, CeraVe, Dermocosmétique Vichy, Galderma Laboratorium GmbH, Eli Lilly, Pfizer, Sanofi Regeneron
Participation in a company sponsored speaker's bureau:	Eli Lilly, Pfizer, Sanofi Regeneron

Scarring and non–scarring alopecia

- Non-scarring: Collapse if IP, regulatory dysfunction around the hair bulb
- Scarring: Collapse of IP, destruction of stem cells around the bulge area





Hair Disorders: Challenges and New Treatment Options

1. Androgenetic alopecia
2. Alopecia areata
3. Primary scarring alopecia

Androgenetic alopecia – Pattern hair loss

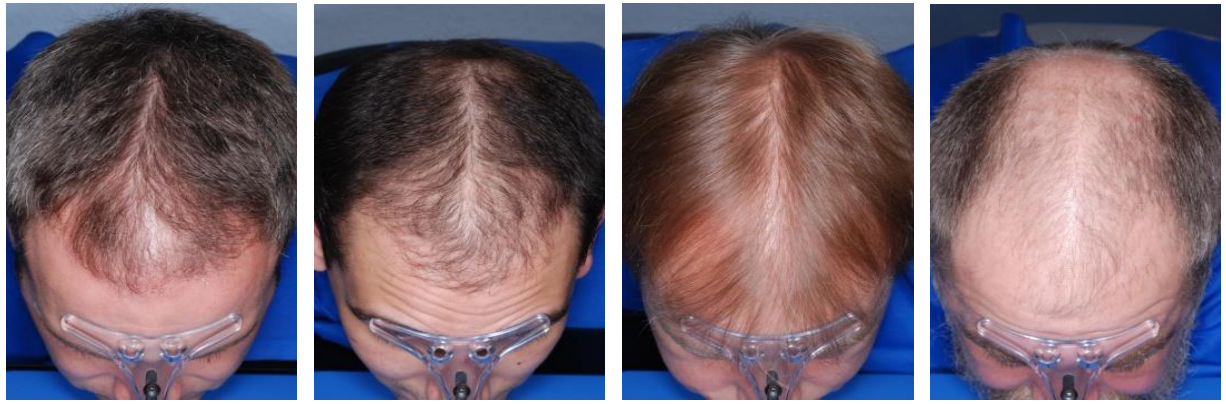
- Male Pattern Baldness – majority
- Female Pattern Hair Loss – seldom
- Onset at any age following puberty
- Increasing frequency with age in all ethnic groups

Prevalence

- Highest in Caucasian, at age 70 or beyond 80%
- Asian 47-60%,
- African American 4 x less common than in Caucasian

Frequent problems and questions in daily practice

- How can I treat my male pattern baldness?
- Anything new?



- Topical finasterid?
- Oral minoxidil?
- Oral minoxidil and 5α-reductase inhibitor?

Androgenetic alopecia – Evidence-based therapy – Men

Therapy	Level of evidence	Efficacy to prevent progression	Efficacy to improve	Safety	Practicality for patient	Practicality for physician
Minoxidil 5 % BID (solution, foam)	1	+++	++	++++	+ / ++	+++
Finasteride 1 mg QD	1	+++	++	+++	++++	++
Dutasteride 0,5 mg QD	1	+++	+++	++	++++	++
Hair transplantation with/without combination treatment	2	-	+++	++	+ intervention +++ long-term	+
LLLT	2	+ / -	+ / -	++	+++	+++
PRP	3	+ / -	+ / -	+	+ / -	+

Kanti V ..., Blume-Peytavi U, J Eur Acad Dermatol Venereol. 2018;32(1):11-22;
https://www.guidelines.edf.one//uploads/attachments/cl262ylye009ulajnpuci9r2i-androgenetic-alopecia-2017-gl.pdf (Letzter Aufruf:

Androgenetic alopecia – „Post-Finasteride-Syndrome (PFS)“

- Past years increasing case reports on PFS
- Persisting symptoms over months to years after stopping oral finasterid
- Sexual dysfunction, loss of libido, depression, suicidal thoughts, fatigue, lowered penis sensibility
  Dutasteride 0.5 mg registered in Europe for treating benign prostatic hyperplasia in 2003

- High social media attention
- Direct search for permanent Betroffenen

Are Hair-Loss Drugs Safe?
Men's Journal - 14.09.2015
But emerging research and a slew of lawsuits suggest that **finasteride** may be more dangerous than previously believed, with side effects — inability to ... Men may have no idea that cognitive side effects would have anything to do with taking a hair-loss pill, particularly if those problems continue **after** they ...

Korea one of the first countries to issue warnings on **finasteride**
Korea Biomedical Review - 05.07.2017
Korea has become one of the first countries to warn the public of the depressive side-effects of finasteride, a hair loss medication, according to the **Post-Finasteride Syndrome** Foundation. The 5-alpha-reductase inhibitor drug, commonly known as Propecia, is an anti-balding drug used for hair loss and ...

Dear Doctor letter (DDL) on finasteride

Risk of sexual dysfunction and psychological disorders (5.7.2018)

Patient should be informed,

- That sexual dysfunction may persist up to > 10 years after stopping finasterid
- To be vigilant to possible mood variations!
- „Anxiety“ as new adverse event (EMA-recommendation)

Androgenetic Alopecia – Topical instead of systemic finasteride ?

Aim

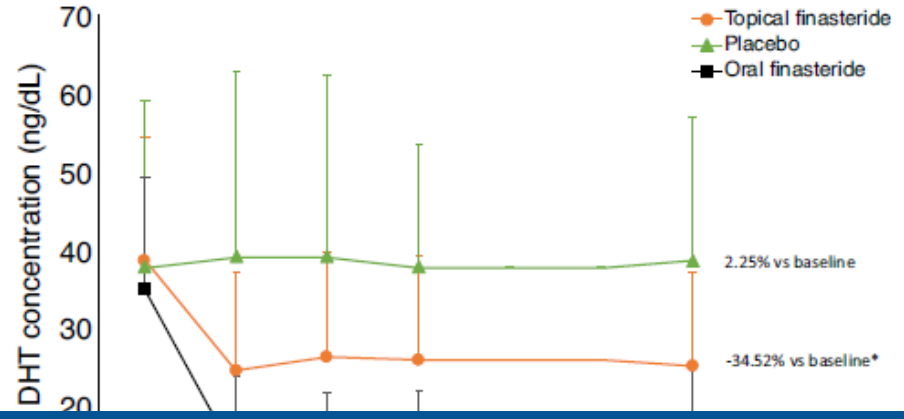
- To obtain locally effective tissue level of finasteride in the scalp with subsequent effective functional inhibition of 5α reductase and effective reduction of DHT level

- Low systemic availability (lower serum level compared to oral application) with preventing or lowering systemic adverse events (e.g. sexual function, etc.)

➢Maximization of efficacy with parallel minimizing systemic adverse events

Androgenetic alopecia – Development of topical finasteride

- RCT- placebo-controlled, 24 weeks, 458 men >18 Jahre, AGA N-H IIIv-V, Europe
- Comparison topical versus oral finasteride versus placebo
- Aim: Maximal effect of hair growth by lowering systemic side effects

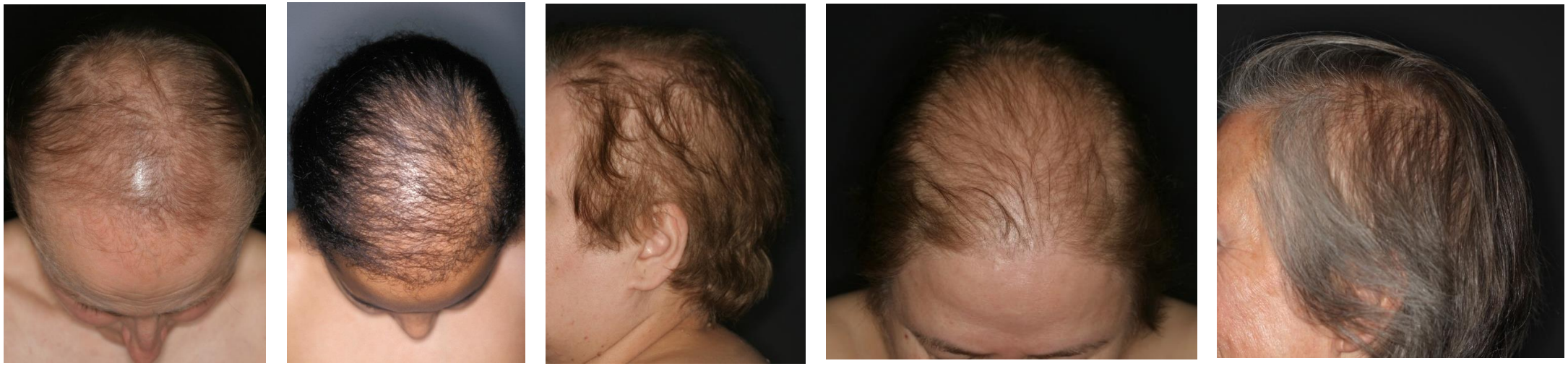


Significant improvement of hair density by topical finasteride vs placebo, good safety profile
Comparable outcome in topical and oral finasteride 1 mg/d, lower finasteride serum level and lower influence of serum DHT level, permission by EMA 2020,

Piraccini BM, Blume-Peytavi U, Scarci F et al. Finasteride topical for male pattern baldness. JEADV 2022, 36, 286–294

Female Pattern Hair Loss in women (FPHL)

- Different clinical presentation and course, different clinical response to treatment



- "Androgenetic alopecia in women" term coined by Ludwig 1977, constantly replaced by term "Female pattern hair loss" (FPHL) to differentiate from AGA in men
  - FPHL mit completely normal hormonal levels
  - FPHL with hormonal dysregulation (small subset)
  - FPHL (with onset of at) Pre-/post-menopause
  - FPHL and senescence alopecia (overlap)

Blume-Peytavi U, Blumeyer A, Tosti A, Finner A, del Marmol V, Trakatelli M, Reygagne P, Messenger A. Br J Dermatol 2011;164(1):5-15

Female Pattern Hair Loss (FPHL) – Evidence-based approach in women

Therapy	Level of evidence	Efficacy to prevent progression	Efficacy to improve	Safety	Practicality for patient	Practicality for physician
Minoxidil 2 % BID solution Minoxidil 5% QD foam	1	+++	++	++++	+	+++
Hormones oral in hyperandrogenism	3	+	+	+	+++	++
Hormones oral in normal hormones	3	+ / -	+ / -	+	+++	++
Hair transplantation	4	-	++	++	+ intervention +++ long-term	+
LLLT	2	+ / -	+ / -	++	+++	+++
PRP	3	+ / -	+ / -	+	+ / -	+

V. Kanti, A. Messenger, G. Dobos, P. Reygagne, A. Finner, A. Blumeyer, M. Trakatelli, A. Tosti, V. del Marmol, B. M. Piraccini, A. Nast, U. Blume-Peytavi. Evidence-based (S3) guideline for the treatment of androgenetic alopecia in women and in men - short version JEADV 2018;32(1):11-22, , www.euroderm.org long version

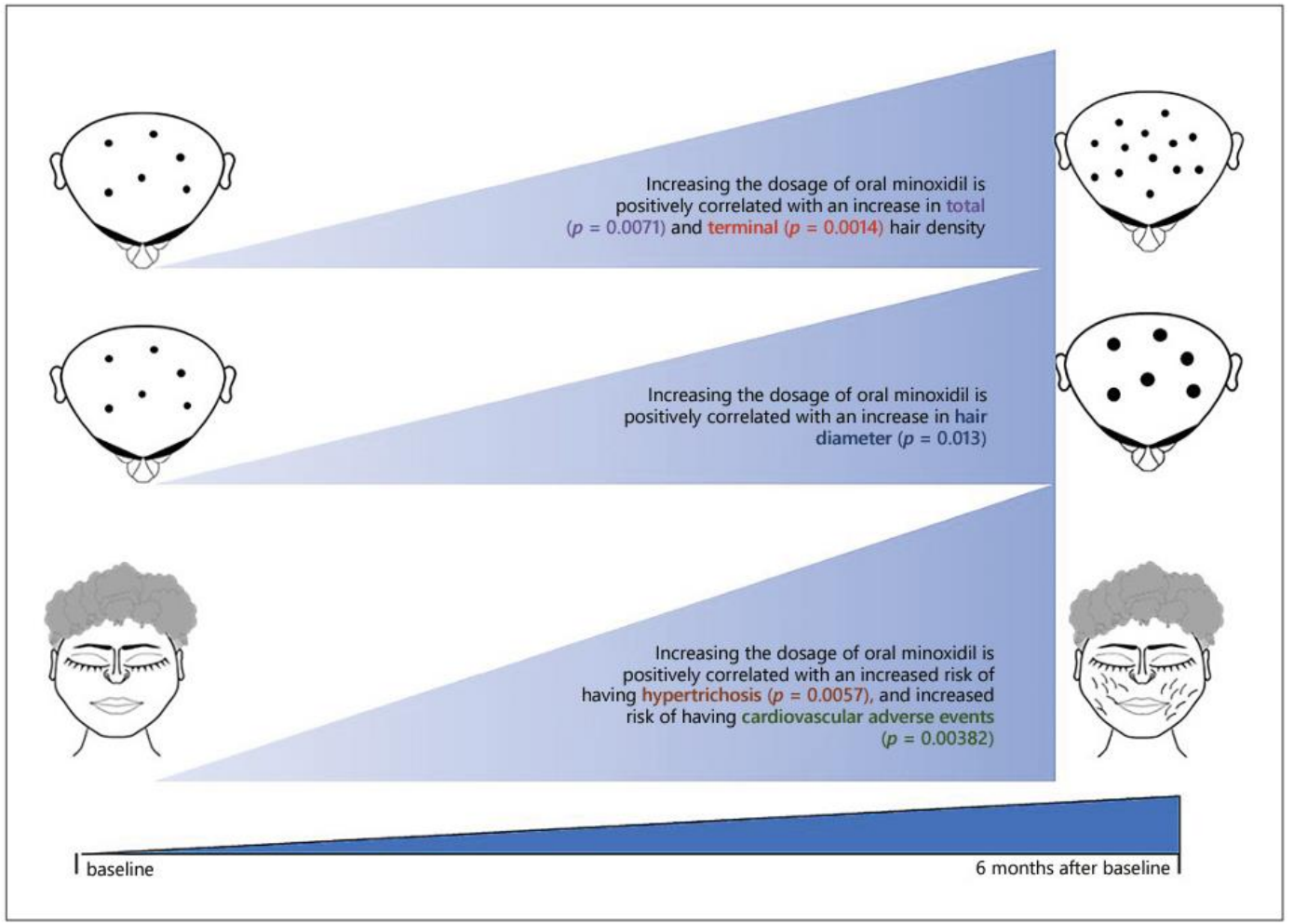
Frequent problems and questions in daily practice

- May I use oral minoxidil for treatment of my pattern hair loss and just take one tablet daily?

- Popular off-label treatment of androgenetic alopecia or female pattern hair loss using low dose oral minoxidil
  (0.5 - 1mg/day in women or 2.5-5 mg/day in men)

Pattern Hair Loss (FPHL) – Low Dose Oral Minoxidil (LDOM)

- LDOM = any dose below 5 mg/day (0,25mg – 5mg, men > women)
- LDOM associated with increase of hair density, hair thickness hypertrichosis and increased risk of cardiovascular side effects
- Young, healthy women with FAGA at 1,25 mg oral minoxidil pericardial and pleural effusion (Trüeb et al. 2022) resp. pericardial, pleural effusion and anasarca (Dlova et al 2022)



Gupta et al. There Is a Positive Dose-Dependent Association between Low-Dose Oral Minoxidil and Its Efficacy for Androgenetic Alopecia: Findings from a Systematic Review with Meta-Regression Analyses. Skin Appendage Disord 2022;8:355–36

Trüeb et al. Serious complication of low-dose oral minoxidil for hair loss. JAAD Case Rep 2022 Dec; 30: 97–98,

Dlova N.C., Jacobs T., Singh S. Pericardial, pleural effusion and anasarca: a rare complication of low-dose oral minoxidil for hair loss. *JAAD Case Reports.* 2022;28:94–96.

AGA or Pattern hair loss: Low Dose Oral Minoxidil (LDOM) – off Label

- Minoxidil rescue anti-hypertensive drug due to ist side effects profile (EKG-abnormalities, tachykardia, pericarditis, edema, hypertrichosis) up-titration from 5 mg up to 20/40 mg/d
- Retrospective investigation (Vano-Galvan et al 2021), no control group: 1404 patients (943 women [67.2 %], 461 men [32.8 %] as AE: headache (1,7 %), edema (1,3 %), tachykardia (0,9 %), hypertrichosis (15,1 %), no severe advers drug events
- Retrospective multicentric study (Moreno-Arrones 2022) on safety of oral minoxidil: Chart review of all treated patients (n = 1700) Jan 2018-October 2020: 12 women with severe AE (mean 46.5 years, 25-73 years) due to wrong compounding of the dose in the pharmacy (problem, most countries do not have e.g. minoxidil as a 2.5 mg tablet available)
- Retrospective multicenter study of patients with hypertension or arrhythmia treated with LDOM for any type of alopecia (n=264) from multiple centers across Brazil and Spain. LDOM treatment showed a favorable safety profile in patients with hypertension or arrhythmia, similar to general population.

Vañó-Galván S et al., J Am Acad Dermatol. 2021;84(6):1644-1651; Moreno-Arrones OM et al., Actas Dermosifiliogr. 2022 Jul-Aug;113(7):725-727. Jimenez-Cauhe J, Safety of Low-Dose Oral Minoxidil in Patients With Hypertension and Arrhythmia: A Multicenter Study of 264 Patients, *Actas Dermosifiliogr.* 2023 Nov 3:S0001-7310(23)00867-0.

Pattern Hair Loss: Low Dose Oral Minoxidil (LDOM) – off label

1. Female Pattern Hair Loss – FPHL

→ Oral minoxidil dosing 0.25 up to 1.25 mg daily

→ Initial dose 0,25/0,5 mg oral minoxidil daily

2. Male Pattern Hair Loss – MPHL

→ Oral minoxidil dosing 2.5 mg bis 5 mg daily

→ Initial dose 1,25 mg oral minoxidil daily for 6 months, only increase if effect not satisfying
(Jha AK et al 2020)

→ Combination of oral minoxidil with 5α-Reductase inhibitor for enhancing outcome
(Jimenez-Cauhe et al 2019)

Jha AK et al. J Am Acad Dermatol. 2020;83:1491–3; Hassiel et al. Indian Dermatol Online J 2022; 13(6): 729–733; Jimenez-Cauhe J et al. J Am Acad Dermatol. 2019;81:648–9

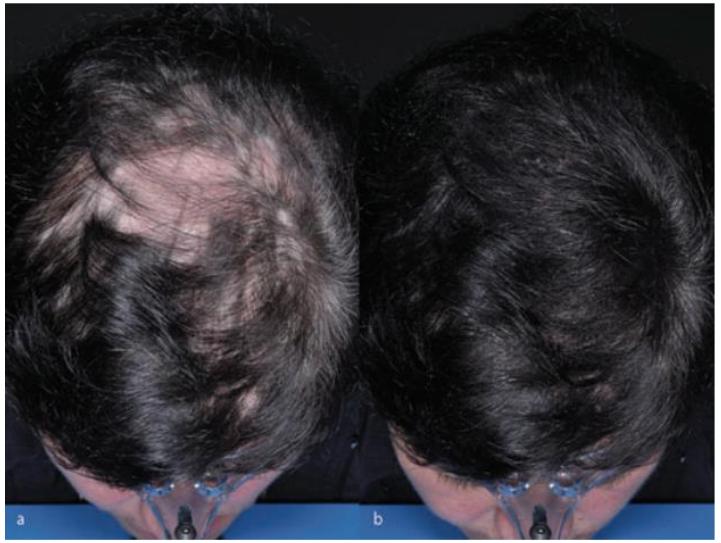
Frequent problems and questions in daily practice

- Does Platelet Rich Plasma (PRP) halt and improve my pattern hair loss?
- How successful is mesotherapy?
- Is it sufficient to use them as a stand-alone treatment?

- PRP, mesotherapy, LLLL therapy - All are part of complementary medicine and should always be combined with an evidence based treatment approach

Androgenetic alopecia – Pattern Hair Loss – Management approach

- Acceptance of genetic trait
  (difficult for women, but also for men)
- Pharmacologic agents
- Non-pharmacologic approaches
- Surgical techniques – hair transplantation
- Cosmetic supportive care
- Psychologic coping strategies
- Esthetic solutions

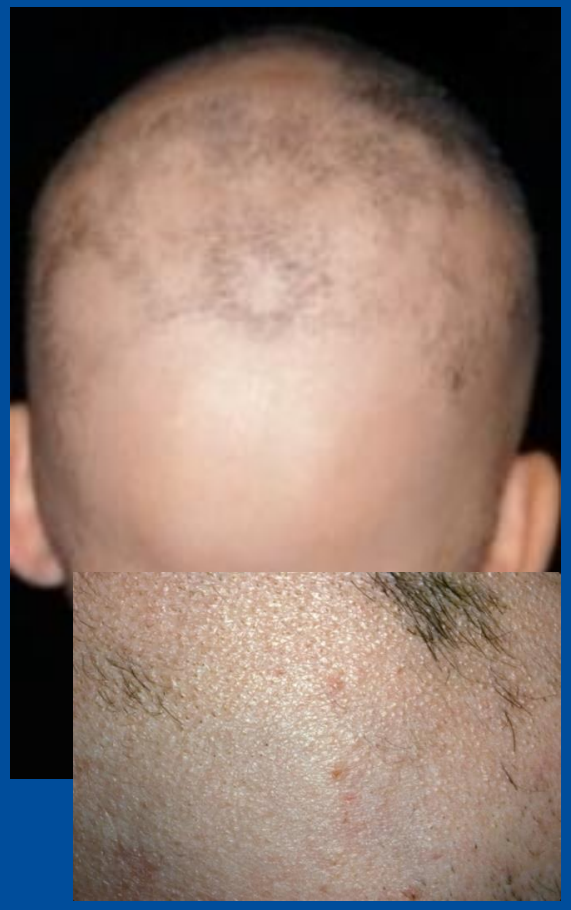


microfiber hair, stray or sprinkle hair

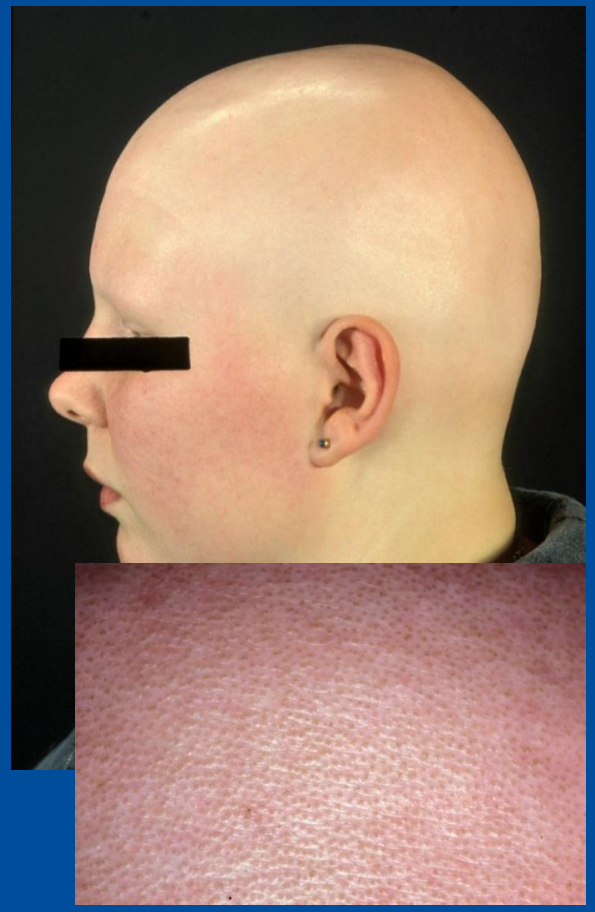
Camouflage with covering spray

Source Blume-Peytavi, Vogt JDDG 2011

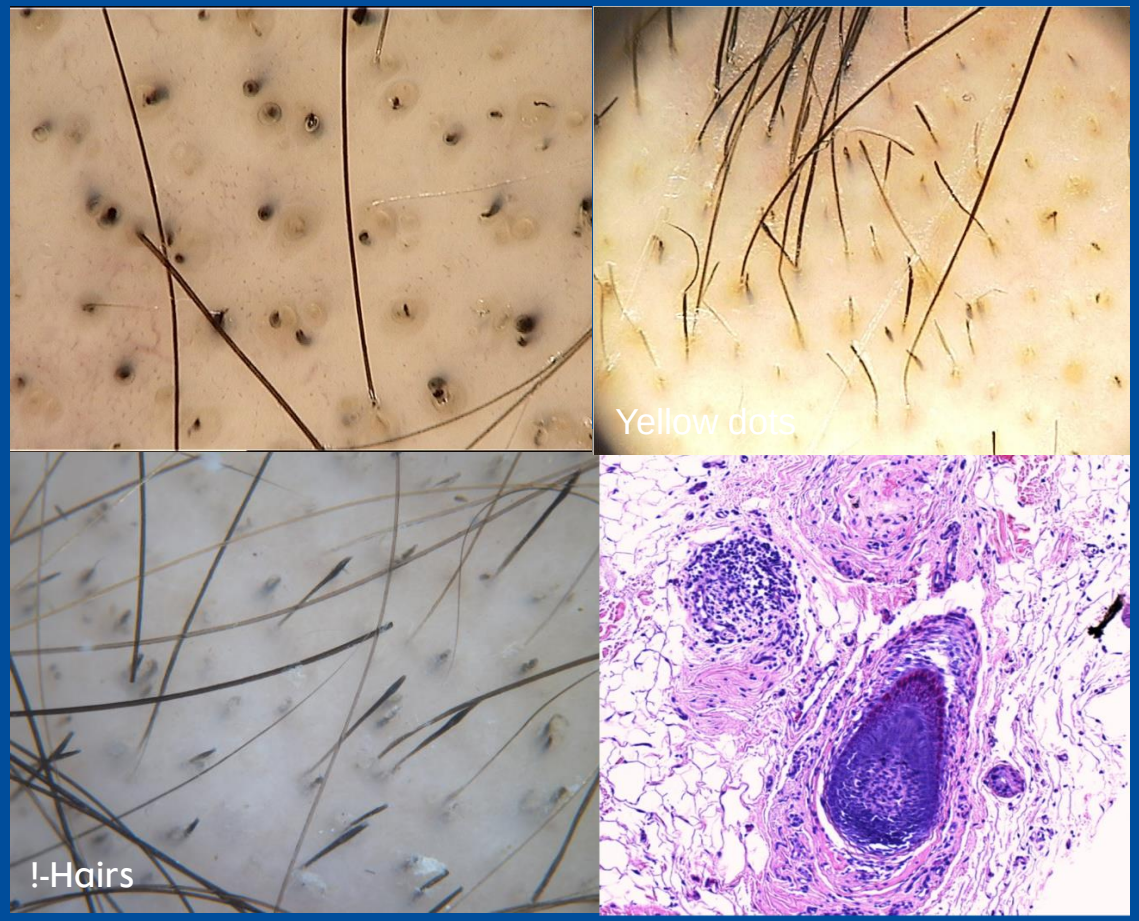
Alopecia areata



Alopecia areata circumscripta



Alopecia areata totalis

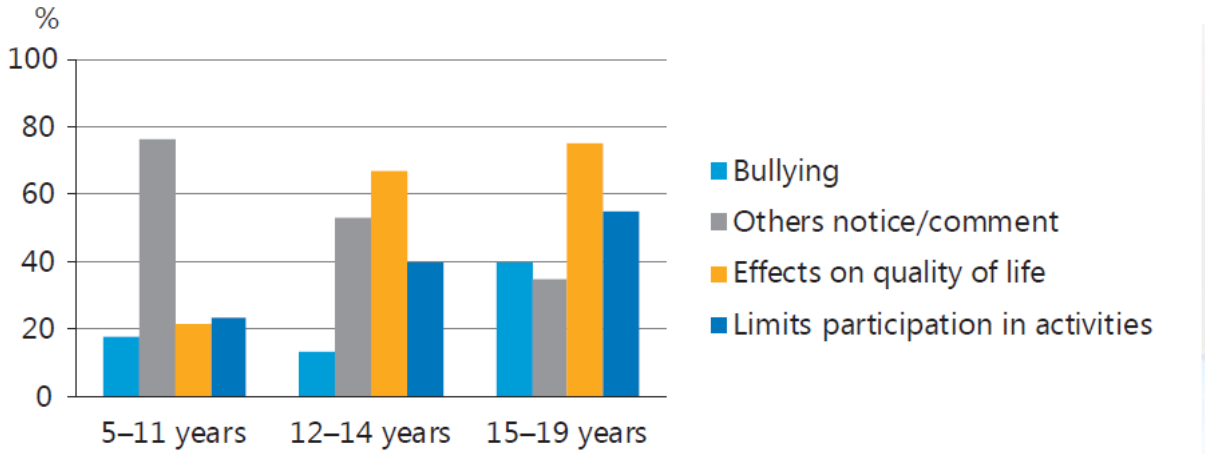


Lintzeri, Constantinou, Hillmann, Vogt, Blume-Peytavi. Alopecia areata JDDG 2022;20(1):59-93

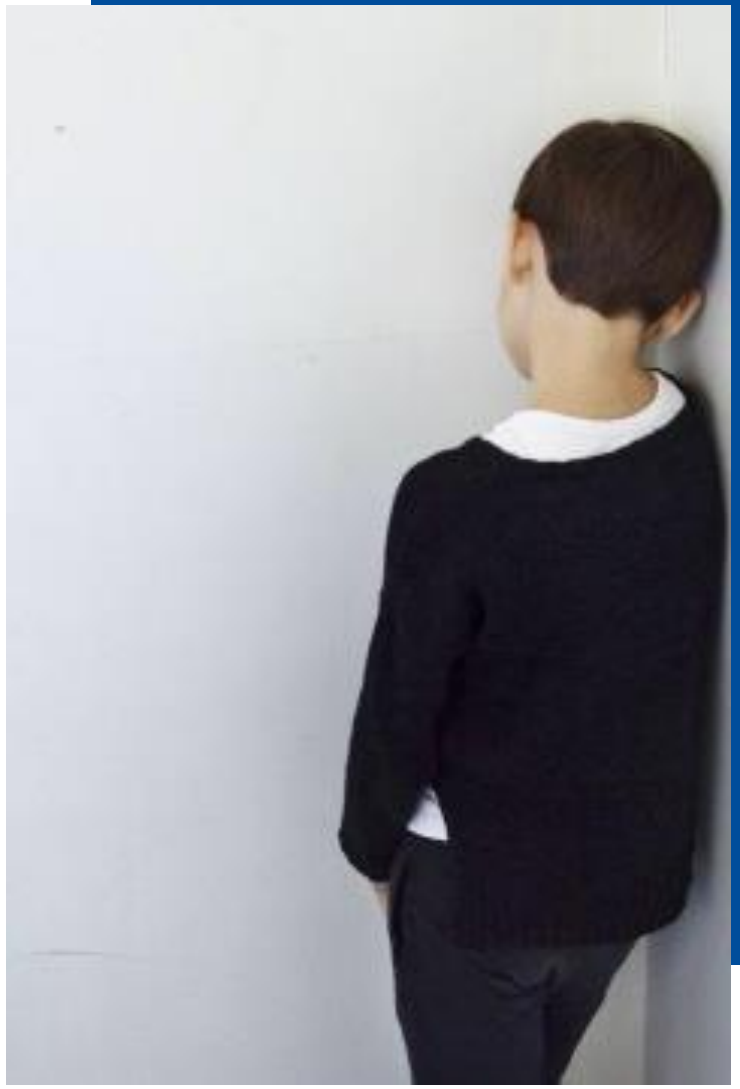
Alopecia areata – Life quality - Emotions

Significant stigmatisation | Bullying | Social isolation and retraction

„a problem“ ?



Age group	Bullying	Others notice/comment	Effects on quality of life	Limits participation in activities
5–11 years	17.647%	76.471%	21.875%	23.529%
12–14 years	13.333%	53.333%	66.667%	40%
15–19 years	40%	35%	75%	50%



Christensen et al. Bullying and Quality of Life in Pediatric Alopecia Areata. Skin Appendage Disord 2017;3:115–118

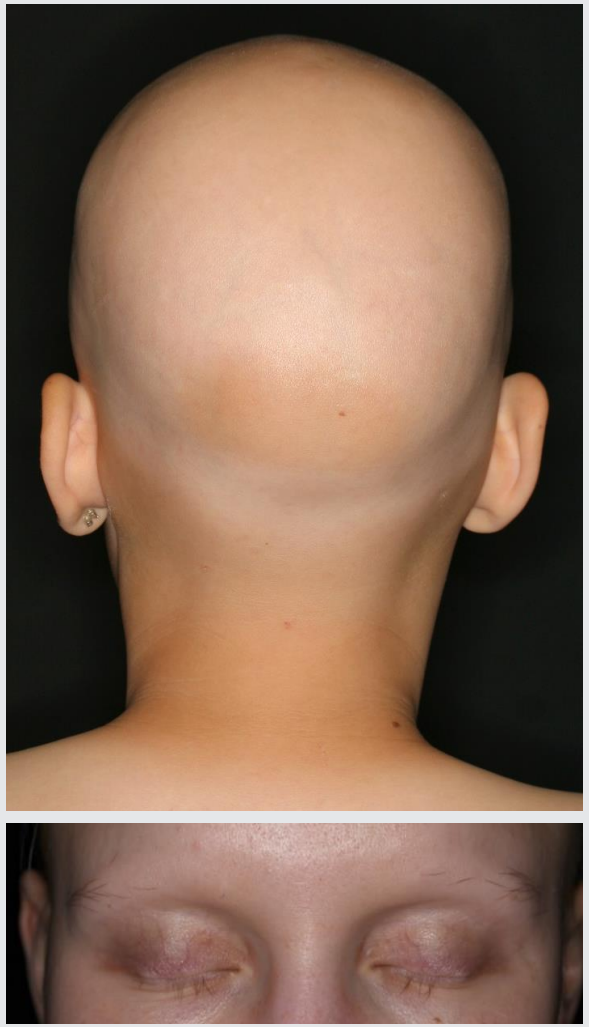
Prendke M, Kanti-Schmidt V, Wilborn D, Hillmann K, Singh R, Vogt A, Kottner J, Blume-Peytavi U. Quality of life in children and adolescents with alopecia areata-A systematic review. J Eur Acad Dermatol Venereol. 2023 Jan 6

Alopecia areata – To treat or not to treat

- ~40% of all AA – patients spontaneous regrowth in first 6 months, 70% show regrowth within 12 months
- Persistence of AA after 12 months: without treatment 30% progress to alopecia totalis (AT) and 15% to alopecia universalis (AU)
- Severe alopecia areata > 50% - 95% SALT Score
- Very severe alopecia areata >95%, AT, AU

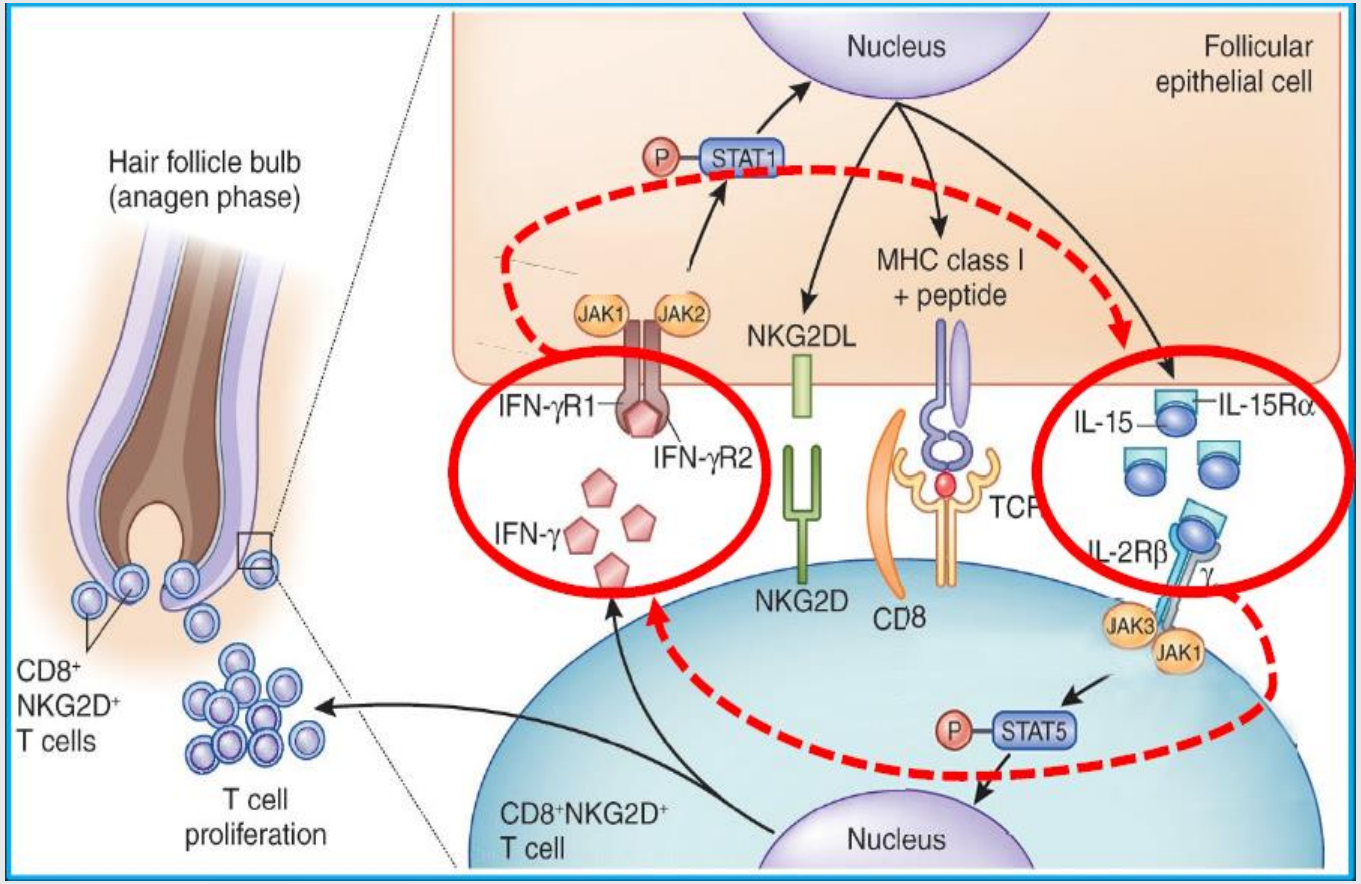
Available therapeutic approaches until recently

- Wait and see – strategy
- Corticosteroids (topical, intralesional, i.v. pulse, continuous)
- Topical minoxidil, methotrexat, cyclosporin A, mycophenolatmofetil, tacrolimus
- DCP (Diphenylcyclopropenon), Cignolin



Lintzeri D, Constantinou, Hillmann K, Ghoreschi K, Vogt A, Blume-Peytavi U. Alopecia areata J Dtsch Dermatol Ges. 2022 Jan;20(1):59-90

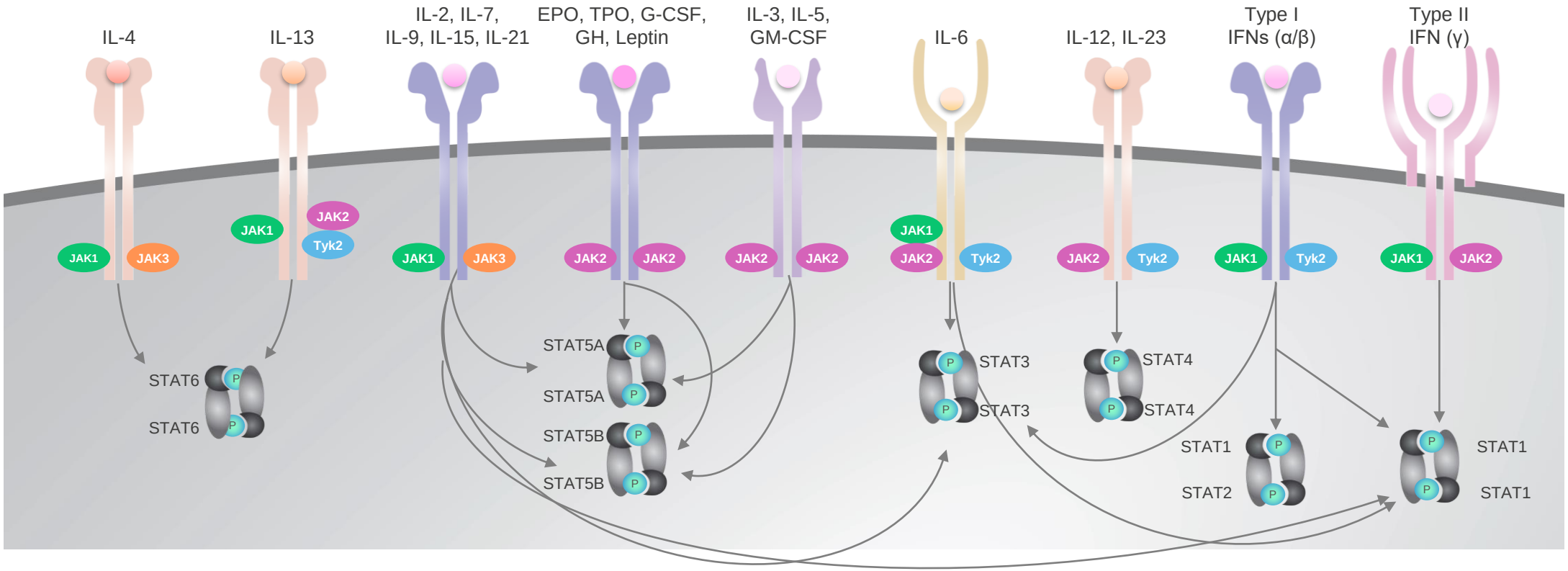
Alopecia areata – Pathogenesis – Immune Privilege



- CD8+ T-cells invade dermis around the hair bulb, produce IFN-γ, which binds to the IFN-γ receptor on the surface of follicular epithelialy cells
- IFN-γ stimulated inflammation is mediated via the JAK-Signalling pathway
- via JAK1/JAK2 signalling synthesis of IL-15 (mediator of CD8+ T-cell actication)
- IL-15 /IL-15-receptor on CD8+T-cells leads to JAK1/JAK3 and IFN-γ production – enhancing the feedback-loop

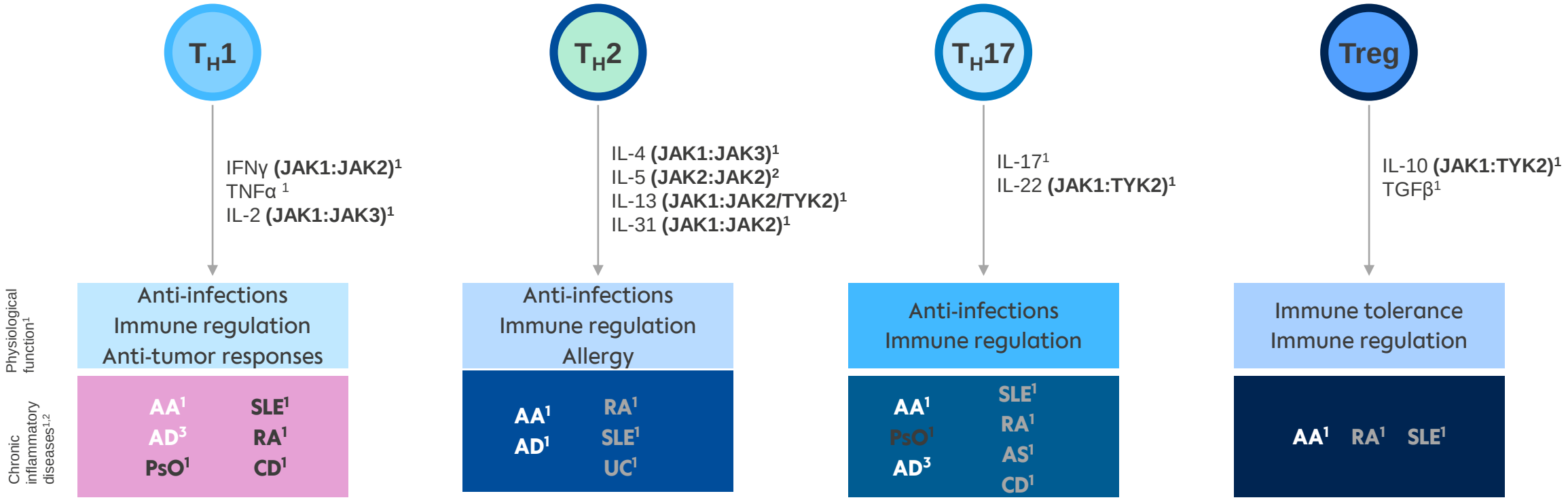
Lintzeri D, Constantinou, Hillmann K, Ghoreschi K, Vogt A, Blume-Peytavi U. Alopecia areata J Dtsch Dermatol Ges. 2022 Jan;20(1):59-90
Divito, S., Kupper, T. Inhibiting Janus kinases to treat alopecia areata. Nat Med 20, 989–990 (2014) https://doi.org/10.1038/nm.3685

Many cytokine receptors signal through different combinations of four JAK and seven STAT family members



EPO, erythropoietin; GH, growth hormone; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte monocyte colony-stimulating factor; gp130, glycoprotein 130; IFN, interferon; IL, interleukin; JAK, Janus kinase; P, phosphorylation; STAT, signal transducer and activator of transcription; TPO, thrombopoietin; Tyk, tyrosine kinase. 1. O'Shea JJ et al. *Annu Rev Med* 2015;66:311-28; 2 Clark JD, et al. *J Med Chem*. 2014 Jun 26;57(12):5023-38. 3.Yuan MG and Wang T. Biomed Rep 2016;5(1):3-6

Janus kinases mediate signaling of multiple cytokines involved in chronic inflammatory diseases (atopic dermatitis, alopecia areata)



Adapted from Virtanen AT, et al[1]

AA, Alopecia areata; AD, Atopic dermatitis; AS, Ankylosing spondylitis; CD, Crohn's disease; IFN, interferon; IL, interleukin; infl., inflammatory; JAK, Janus kinase; PsO, Psoriasis; RA, Rheumatoid arthritis; SLE, Systemic lupus erythematosus; TGF, transforming growth factor; T_H, T-helper cell; TNF, tumor necrosis factor; Treg, T-regulatory cell; TYK, tyrosine kinase; UC, Ulcerative colitis

Data taken from 1. Virtanen AT, et al. BioDrugs 2019;33(1):15-32; 2. Gadina M, et al. Rheumatology 2019;58:i4i16; 3. Czarnowicki T, et al. *J Allergy Clin Immunol*. 2019 Jan;143(1):1-11.

Alopecia areata – Clinical Studies

Name des Medikaments	Hemmung	FDA- Zugelassene Indikationen	EMA-Zugelassene Indikationen	Studie				
				Gabe	Ausprägungen	Phase	Studiennummer	Status
Tofacitinib	JAK1, JAK3	RA, PsA, Colitis ulcerosa	RA, PsA, Colitis ulcerosa, pJIA	Oral	AA	IV	NCT03800979	Abgeschlossen
					AA, AT, AU	K.A.	NCT02312882	Abgeschlossen
						II	NCT02299297	Abgeschlossen
						II	NCT02197455	Abgeschlossen
				topisch		II	NCT02812342	Abgeschlossen
Ruxolitinib	JAK1, JAK2	Myelofibrose, Polyzythämie vera, aGVHD, cGVHD	Myelofibrose, Polyzythämie vera	topisch	AA, AT, AU	II	NCT02553330	Beendet
				Oral	AA	II	NCT01950780	Abgeschlossen
Baricitinib	JAK1 JAK2	RA, COVID-19[1]	RA, AD	Oral	AA, AT	III	NCT03899259	Aktiv, nicht rekrutierend
						II/III	NCT03570749	Aktiv, nicht rekrutierend
CTP-543 (deuteriertes Ruxolitinib)	JAK1 JAK2	-	-	Oral	AA, AT	III	NCT04797650	Rekrutierung
						II	NCT03941548	Abgeschlossen
						II	NCT04784533	Rekrutierung
						II	NCT03811912	Abgeschlossen
						III	NCT04518995	Rekrutierung
						II/III	NCT03898479	Rekrutierung
						II	NCT03137381	Abgeschlossen
PF-06651600	JAK3	-	-	Oral	AA, AT, AU	II	NCT04517864	Aktiv, nicht rekrutierend
						III	NCT04006457	Rekrutierung
						III	NCT03732807	Abgeschlossen
					AA, AT	II	NCT02974868	Abgeschlossen
PF-06700841	JAK1 TYK2	-	-	Oral	AA, AT	II	NCT02974868	Abgeschlossen
Jaktinib-Hydrochlorid	JAK1 JAK2 JAK3	-	-	Oral	AA, AT	II	NCT04034134	Rekrutierung
LEO 124249 (Delgocitinib)	PanJAK	-	-	topisch	Augenbraue AA	II	NCT03325296	Beendet
					AA, AT, AU	II	NCT02561585	Abgeschlossen
ATI-501	JAK1 JAK3	-		Oral	AA, AT, AU	II	NCT03594227	Abgeschlossen
ATI-502	JAK1 JAK3	-	-	topisch	AA, AT, AU	II	NCT03759340	Beendet
ATI-50002	JAK1 JAK3	-		topisch	AA	II	NCT03354637	Beendet
					Augenbraue AA	II	NCT03551821	Abgeschlossen
					AT, AU	II	NCT03315689	Abgeschlossen

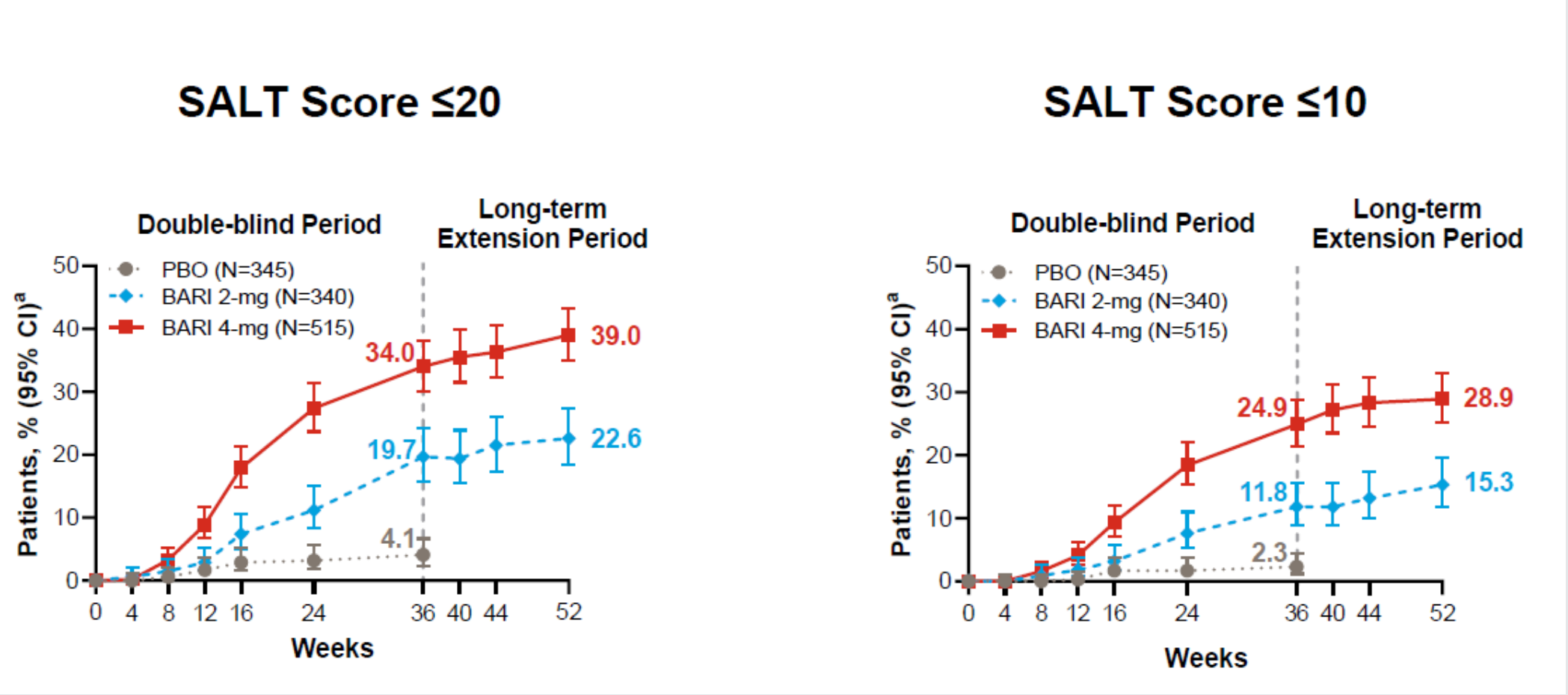
Lintzeri D, Constantinou, Hillmann K, Ghoreschi K, Vogt A, Blume-Peytavi U. Die Alopecia areata J Dtsch Dermatol Ges. 2022 Jan;20(1):59-90

Alopecia areata | New Treaments

Baricitinib
FDA and EMA approval
06/2022

Alopecia areata – Baricitinib 2 und 4 mg vs Placebo

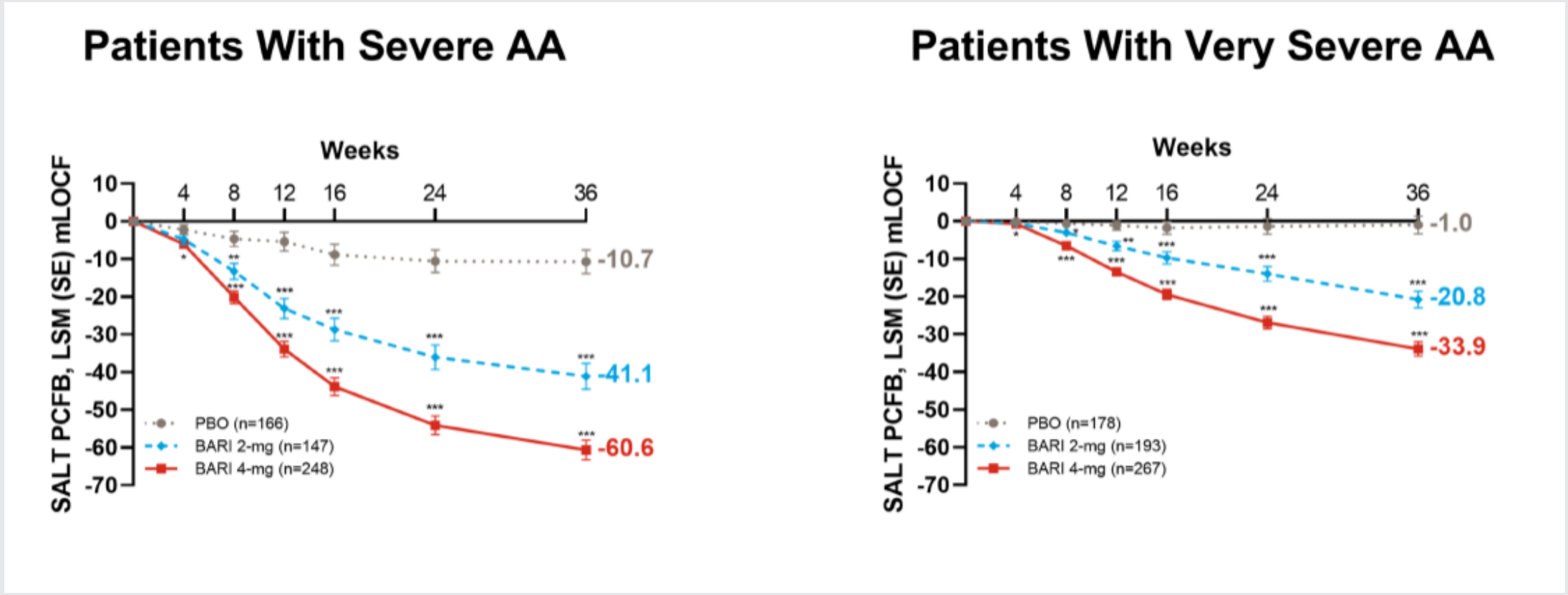
Patients with SALT Score ≤ 20 and < 10



Poster presentation AAD 2022

Alopecia areata – Baricitinib 2 und 4 mg vs Placebo

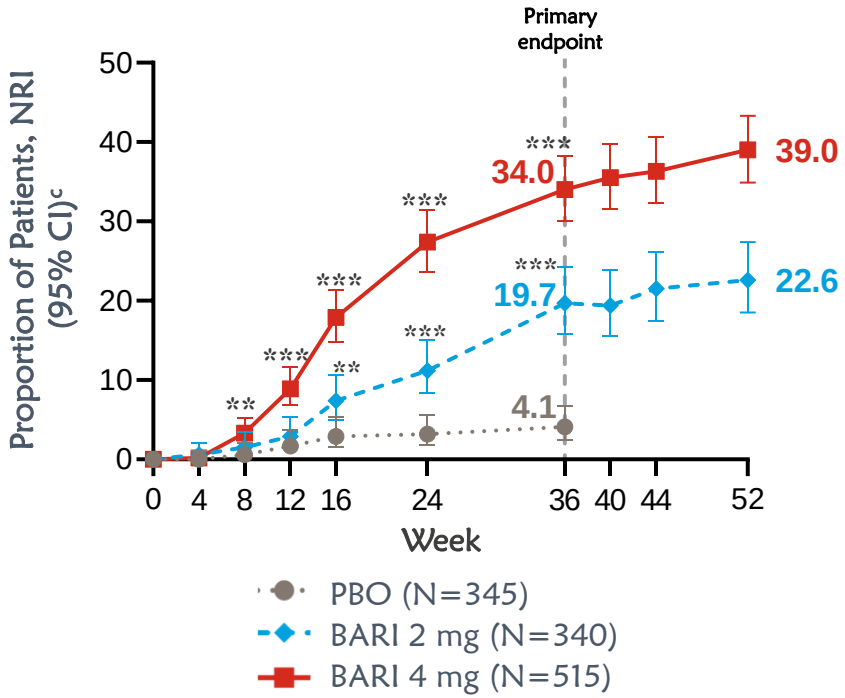
Better outcome in patients with severe AA than in very severe AA



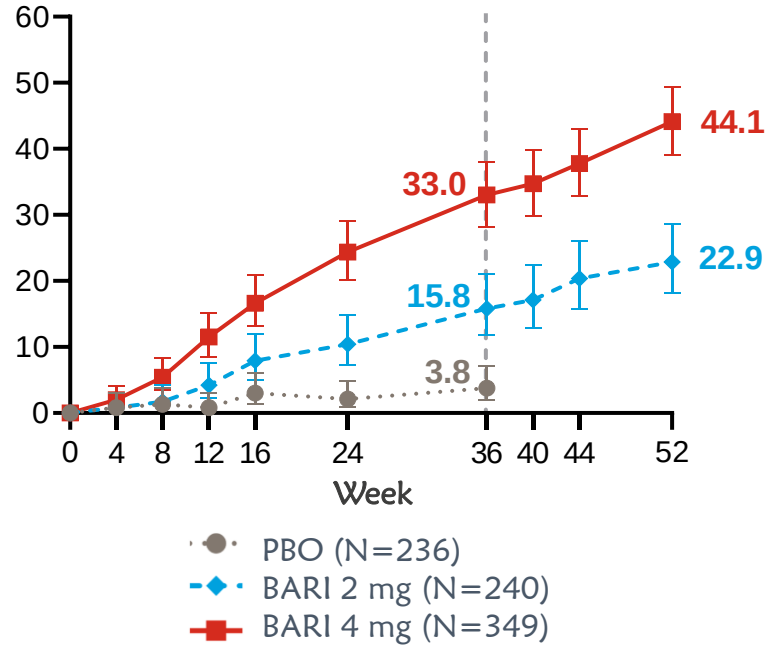
Poster presentation AAD 2022

Baricitinib 4 mg more effective than the 2 mg dose for the primary endpoint and most of the key secondary endpoints

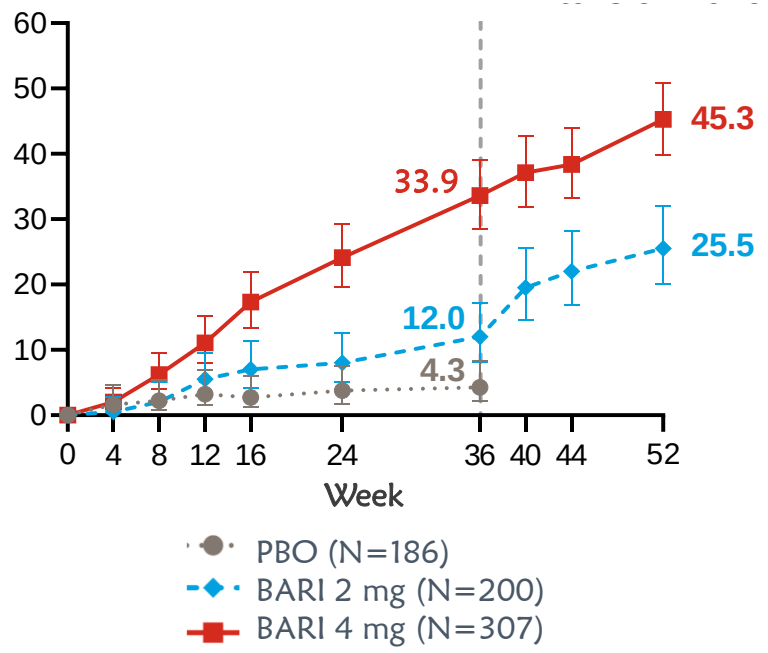
Pooled data[1] – SALT ≤20[a]



Pooled data[1] – ClinRO EB[b]



Pooled data[1] – ClinRO EL[b]



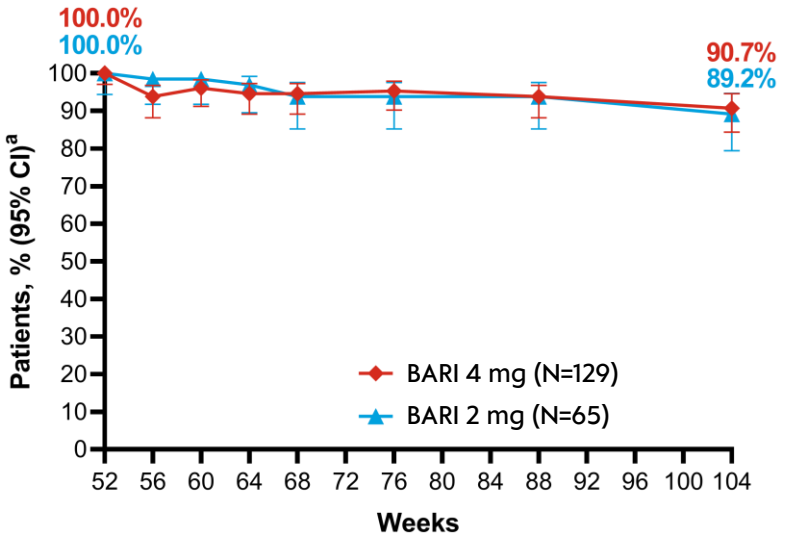
Note: p-value vs. PBO ***p≤0.001; **p≤0.01. Patients randomised to BARI 2 mg or BARI 4 mg at baseline retained treatment allocation through Week 52, whereas PBO non-responders were rescued at Week 36.
[a]80% or more scalp coverage with hair. [b]Full coverage or minimal gaps with ≥2 improvement from baseline and among patients with a ClinRO EB/EL ≥2 at baseline. [c]CIs are constructed using the Wilson method, without continuity correction.
BARI=baricitinib; CI=confidence interval; ClinRO=clinician-reported outcome; EB=eyebrow; EL=eyelash; NRI=non-responder imputation; PBO=placebo; SALT=Severity of Alopecia Tool.

1. Kwon O, et al. Oral presentation presented at American Academy of Dermatology (AAD); March 25–29, 2022. Abstract LB. 2. Baricitinib EPAR Assessment Report 572597. 2022. Available at https://www.ema.europa.eu/documents/variation-report/olumiant-h-c-4085-ii-0029-g-epar-assessment-report-variation_en.pdf (accessed September 2023).

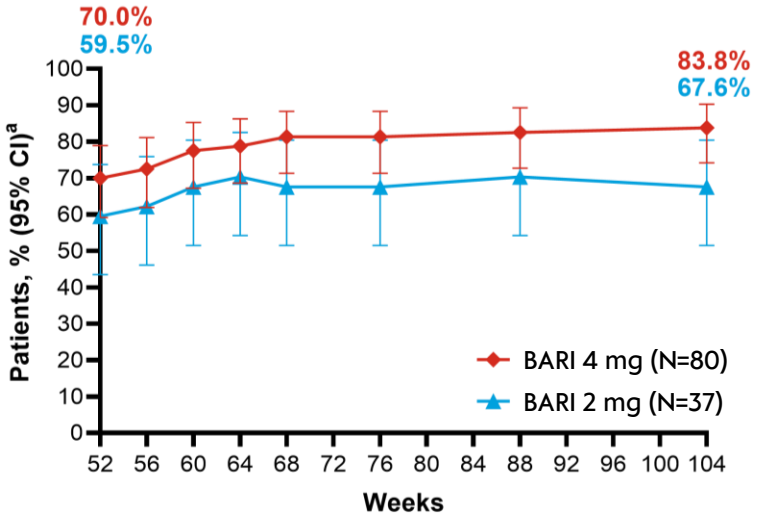
Clinically meaningful scalp hair regrowth maintained through Week 104

in ~90% of patients treated with baricitinib 4 mg or 2 mg with response at Week 52

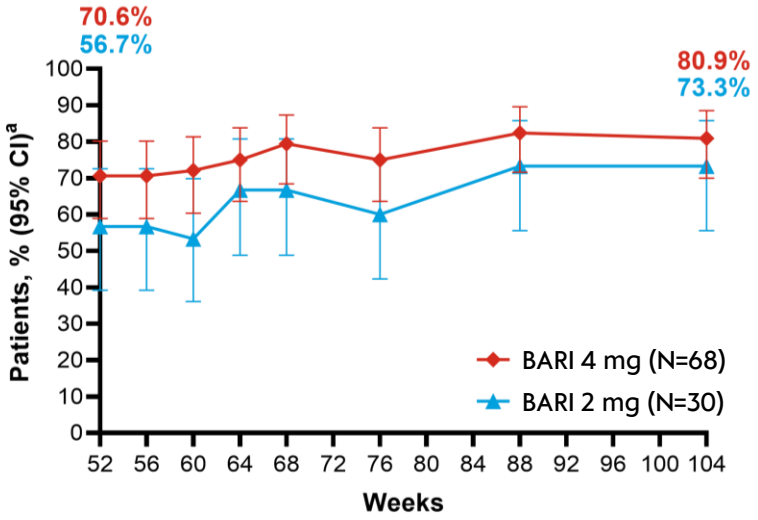
Proportion of Week 52 responders who achieved SALT score ≤20 through Week 104



Proportion of Week 52 responders[a] with ClinRO EB ≥2 at baseline who achieved ClinRO EB (0,1)[b] through Week 104



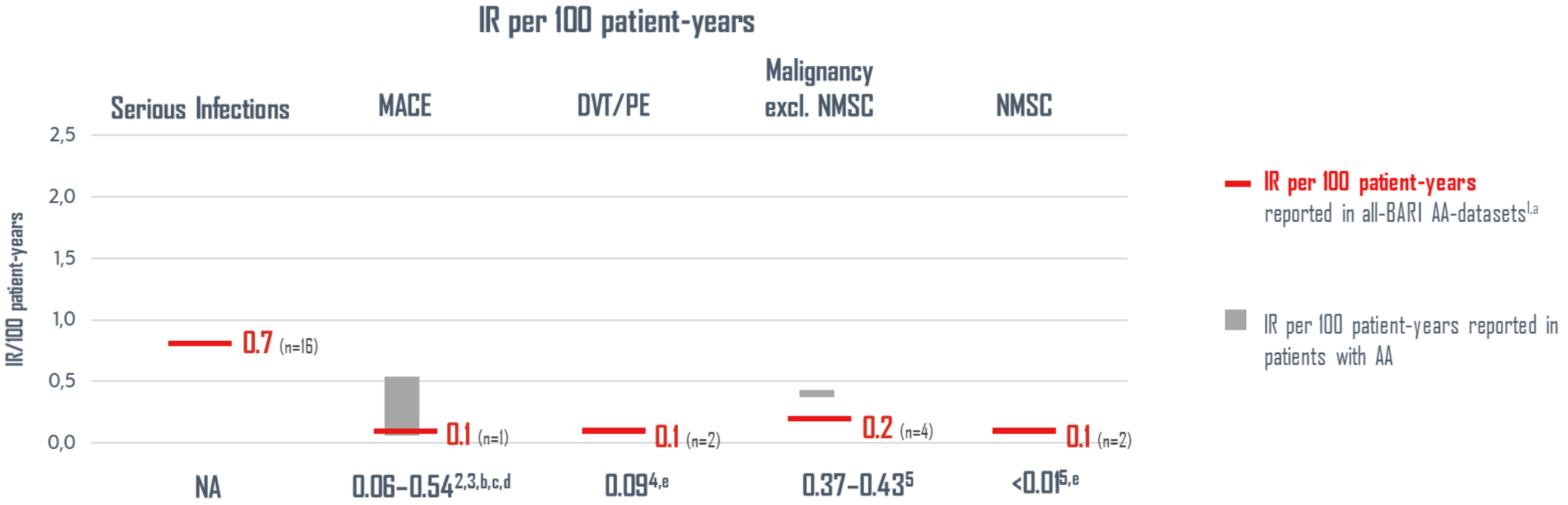
Proportion of Week 52 responders[a] with ClinRO EL ≥2 at baseline who achieved ClinRO EL (0,1)[b] through Week 104



Eyebrow and eyelash growth continued to improve through 104 weeks

[a]BARI 4 mg-treated and 2 mg-treated patients with SALT score ≤20 at Week 52. [b]With ≤2-point improvements from baseline. Note: Data were summarised with mLOCF imputation.BARI=baricitinib; CI=confidence interval; mLOCF=modified last observation carried forward; SALT=Severity of Alopecia Tool. Senna MM, et al. Long-term efficacy of baricitinib in alopecia areata: 104-week results from BRAVE-AA1 and BRAVE-AA2. Poster presented at American Academy of Dermatology (AAD); March 17–21, 2023.

Rates of events of special interest reported with baricitinib generally reflected the underlying risk of the alopecia areata patient population



Baricitinib IRs of serious infections, MACE, DVT/PE and malignancies are seen to be within the background rates in AA

[a]Rates in patients treated with ≥1 dose of baricitinib across 2 randomized, controlled trials; 1303 patients received baricitinib for 2218 patient-years of exposure (median exposure: 1.6 years; maximum exposure: 3.6 years). [b]Composite endpoint of MACE not available for patients with AA from published literature. [c]Myocardial infarction rate from Korean National Health Insurance claims database. [d]Stroke rate from Taiwanese Longitudinal Health Insurance Database 2000. [e]Grey bar representing background IR overlaps with red bar representing baricitinib IR.
AA=alopecia areata; BARI=baricitinib; DVT=deep vein thrombosis; IR=incidence rate; MACE=major adverse cardiovascular event; n=number of patients in specified category; NA=not available; NMSC=non-melanoma skin cancer; PE=pulmonary embolism.
1. King B, et al. Poster 43018 presented at American Academy of Dermatology (AAD); March 17–21, 2023. 2. Shin J-W, et al. JAMA Dermatol. 2020;156(7): 763–771. 3. Kang J-H, et al. Sci Rep. 2015;5: 11718. 4. Schneeweiss MC, et al. JAMA Dermatol. 2021;157(7): 805–881. 5. Bieber T, et al. Adv Ther. 2022;39(11): 4910–4960. 6. George P, et al. Dermatol Ther (Heidelb). 2023;13(8): 1733–1746.

Alopecia areata | New Treament

Ritlecitinib
FDA and EMA approval
09/2023

Ritlecitinib – Dual MoA targets Key Immune System-activating Interactions in AA[1–9]

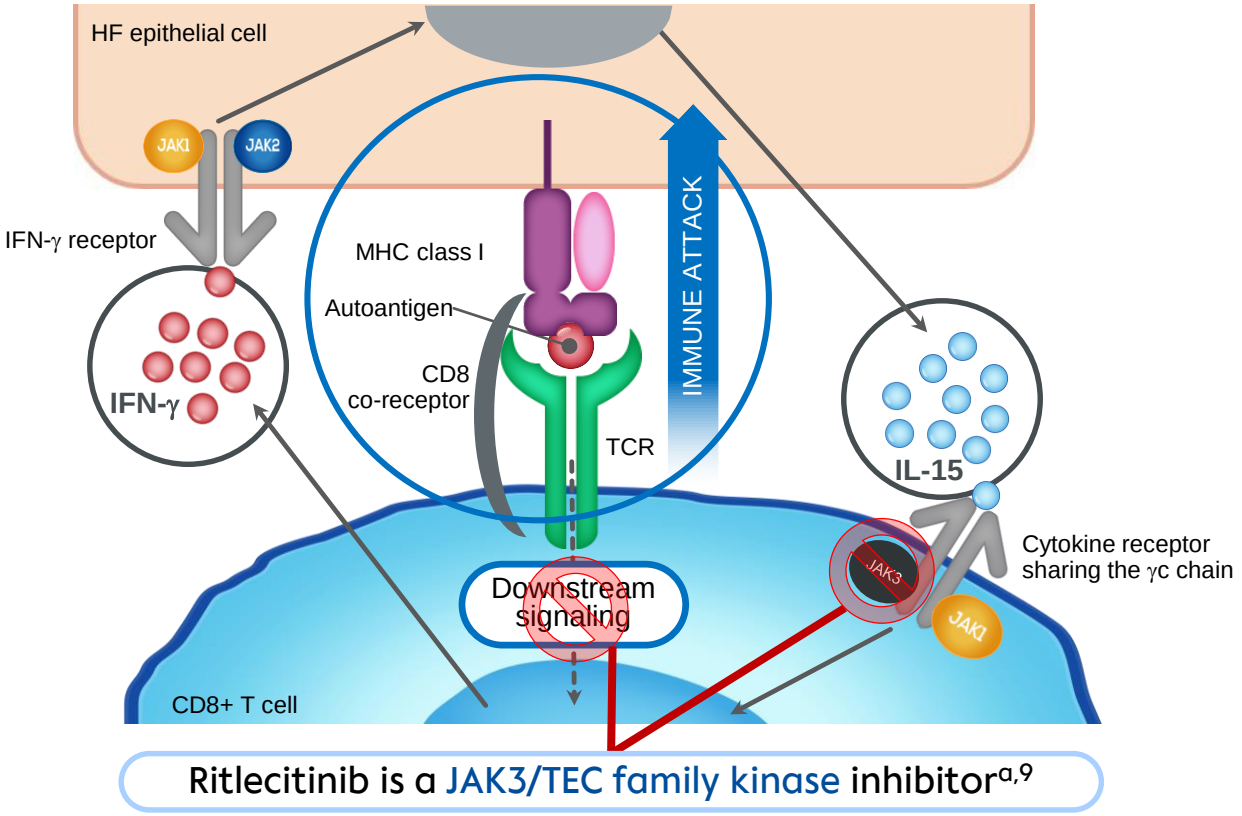


Figure adapted from Divito SJ, Kupper TS. 2014.[4]

IFN-γ and IL-15 are important drivers of AA[1,2]

- Perpetrate an inflammatory positive feedback loop[2,4]
- Signal through JAK1, JAK2, and JAK3[2]

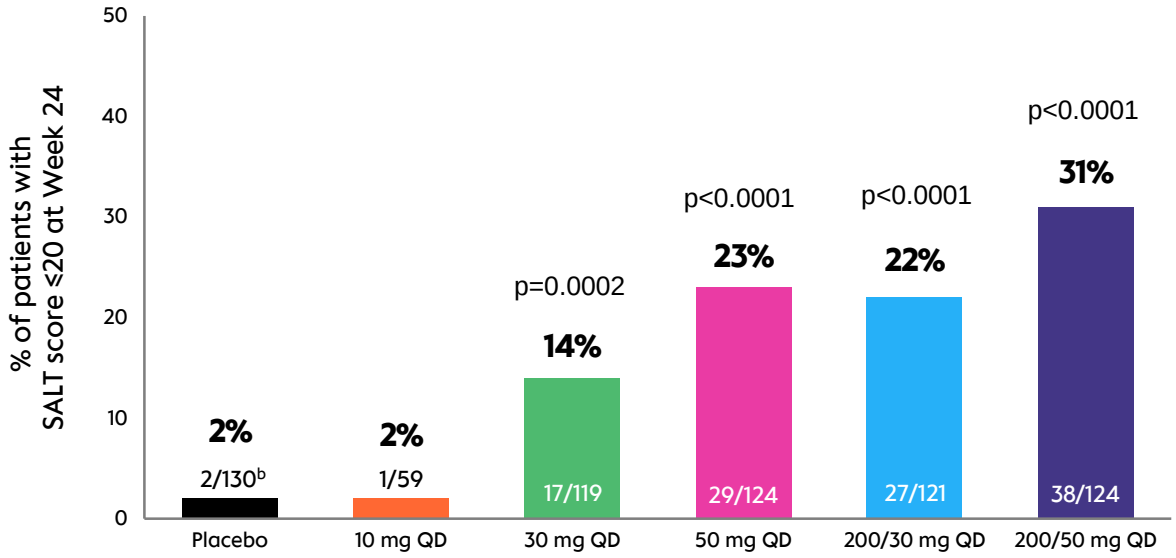
- Immune attack by CD8+ T cells is understood to require autoantigen recognition by the TCR[3,5,6]
- Three members of the TEC family of kinases are involved in signaling downstream of the TCR: TEC, ITK, and TXK[7]
- Notably, in the scalp of patients with AA, a specific TCR signaling signature including ITK has been shown in activated T cells[8]

•[a]Five kinases of the TEC family are inhibited (TEC, BTK, ITK, BMX, and TXK).[9,10]

1. Gilhar A, Paus R, Kalish RS. *J Clin Invest.* 2007;117(8): 2019–27. 2. Xing L, et al. *Nat Med.* 2014;20(9):1043–9. 3. Paus R, et al. *J Investig Dermatol Symp Proc.* 2003;8(2):188–94. 4. Divito SJ, Kupper TS. *Nat Medicine.* 2014;20(9):989–90. 5. Wang EHC, et al. *J Invest Dermatol.* 2016;136(8):1617–26. 6. King B, et al. *Lancet.* 2023 [In Press, doi: 10.1016/S0140-6736(23)00222-2]. 7. Schwartzberg PL, Finkelstein LD, Readinger JA. *Nat Rev Immunol.* 2005;5(4):284–95. 8. Smith SE, et al. *Sci Signal.* 2016;9(439):rs7. 9. Xu H, et al. *ACS Chem Biol.* 2019;14(6):1235–42. 10. National Library of Medicine. TXK. Available at: www.ncbi.nlm.nih.gov/gene/7294 [Last accessed April 2023].

Alopecia areata: Ritlecitinib (JAK3, TYKi) – Efficacy

At week 24, significantly higher proportion of patients with a SALT score ≤20[a] across all ritlecitinib doses tested compared with placebo



The difference in response rate based on SALT score ≤20 between placebo and ritlecitinib was:

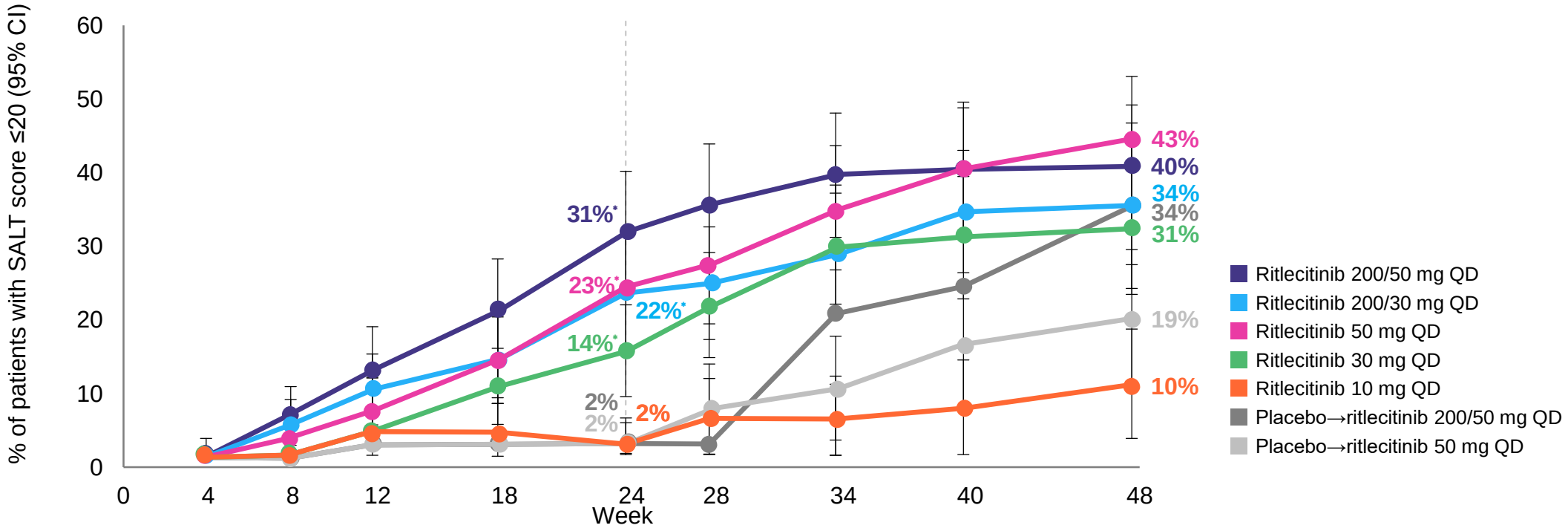
- 12.8% (95% CI: 6.7, 20.4; p=0.0002) for the 30 mg group
- 21.9% (95% CI: 14.7, 30.2; p<0.0001) for the 50 mg group
- 20.8% (95% CI: 13.7, 29.2; p<0.0001) for the 200/30 mg group
- 29.1% (95% CI: 21.2, 37.9; p<0.0001) for the 200/50 mg group

•[a]Primary endpoint for overall clinical study (α=0.05) and for the FDA (α=0.00125). Miettinen and Nurminen method was used to calculate 95% CIs and Farrington-Manning method was used to calculate p-values for testing the difference in the proportion of response between each active treatment group and placebo. Data missing due to COVID-19 were excluded from this analysis, whereas patients with missing data due to other reasons were included in the analysis as non-responders. [b]Both placebo groups were combined for Week 24 analyses.

1. King B. et al., Lancet 2023; 401: 1518–29.

Alopecia areata: Ritlecitinib (JAK3, TYKi) – Efficacy

SALT score ≤20 response continued to increase through to Week 48 across all Ritlecitinib doses tested[a,1,2]



- [a]Ritlecitinib 200/50 mg, 200/30 mg, 50 mg, and 30 mg QD.
- Vertical bars represent 95% CIs.[1,2] *Statistically significant vs placebo for the overall study and at an overall significance level (α) of 0.05.[1,2]
- 1. King B. et al., Lancet 2023; 401: 1518–29.. 2. Supplemental appendix to 1. King B. et al., Lancet 2023; 401: 1518–29

Alopecia areata: Ritlecitinib (JAK3, TYKi) – Tolerability

Summary of AEs, SAEs and Discontinuations up to Week 48 + F/U Period (SAS)

Patients with AE, n (%)	Placebo→ 50 mg QD (n=66)	Placebo→ 200/50 mg QD (n=65)	10 mg QD (n=62)	30 mg QD (n=132)	50 mg QD (n=130)	200 mg then 30 mg QD (n=129)	200 mg then 50 mg QD (n=131)
Permanent discontinuations due to AEs	4 (6)	0	2 (3)	6 (5)	4 (3)	2 (2)	4 (3)
Temporary dose interruptions due to AEs	8 (12)	13 (20)	5 (8)	16 (12)	20 (15)	16 (12)	17 (13)
Patients with AEs	57 (86)	54 (83)	47 (76)	106 (80)	110 (85)	105 (81)	108 (82)
AEs occurring in ≥10% of patients[a]							
Headache	8 (12)	8 (12)	12 (19)	24 (18)	16 (12)	14 (11)	17 (13)
Nasopharyngitis	4 (6)	7 (11)	7 (11)	21 (16)	18 (13)	21 (16)	19 (15)
URTI	6 (9)	7 (11)	2 (3)	16 (12)	11 (8)	12 (9)	18 (14)
Nausea	1 (2)	8 (12)	3 (5)	12 (9)	3 (2)	3 (2)	11 (8)
Acne	8 (12)	5 (8)	3 (5)	12 (9)	12 (9)	10 (8)	6 (5)
Patients with SAEs	3 (5)	0	2 (3)	1 (1)	2 (2)	2 (2)	4 (3)

[a]Individual AEs (by preferred term) reported in ≥10% of patients in a given treatment group during the indicated period.

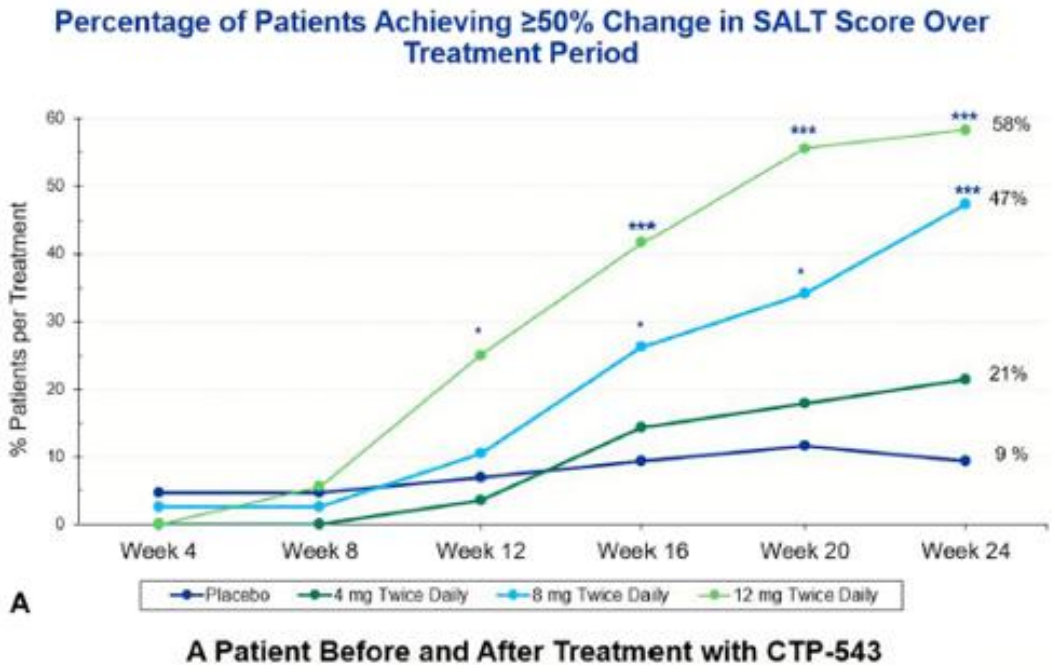
1. King B. et al., Lancet 2023; 401: 1518–29.

Alopecia areata | New Treament

Deuruxolitinib – in clinical trials

Selektive Jak-Inhibitor (Deuruxolitinib) in moderate to severe alopecia areata

Phase 2 RCT – dose finding study



King B et al. J Am Acad Dermatol https://doi.org/10.1016/j.jaad.2022.03.045

Alopecia areata | New Treament

JAK – Inhibitors – Side effects

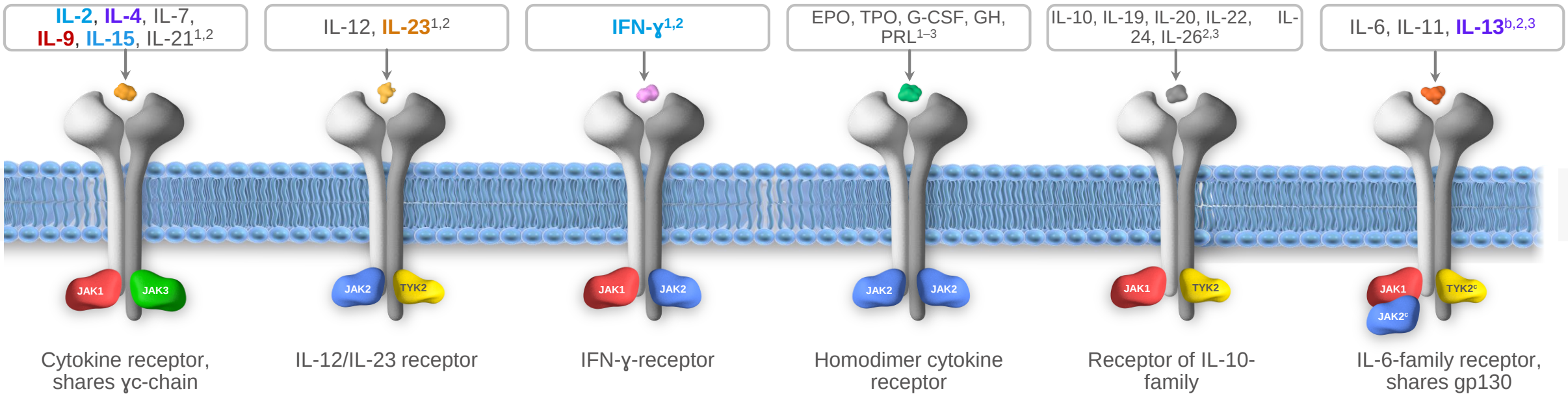
JAK Inhibitors in Immune-Mediated Inflammatory Skin Diseases

Side effects and Cardiovascular and Venous Thromboembolic Risk

- FDA boxed warning label for oral and topical JAK inhibitors (class) increased risk of major adverse cardiovascular events (MACE), venous thromboembolism (VTE), serious infections, malignant neoplasm, and death (Boxed warning as results of the Oral Rheumatoid Arthritis Trial (ORAL) Surveillance study, only patients with rheumatoid arthritis
- Systematic review and meta-analysis : 35 randomized clinical trials containing over 20 000 patients with dermatologic conditions, no significant difference was found between JAK inhibitors and placebo/active comparator in composite MACE and all-cause mortality or VTE
- Limitations: Mean follow-up time was 4.9 months, so the association of long-term use of JAK inhibitors is unknown
- Additional trials with long-term follow-up are needed to better understand the safety risks of JAK inhibitors used for dermatologic indications

Ingrassia, JP et al. Cardiovascular and Venous Thromboembolic Risk With JAK Inhibitors in Immune-Mediated Inflammatory Skin Diseases A Systematic Review and Meta-Analysis. JAMA Dermatol. doi:10.1001/jamadermatol.2023.4090, November 1, 2023

Alopecia areata – Targeted Therapy



- Baricitinib selective JAK1 + JAK2i (EMA June 2022)
- Ritlecitinib dual kinase-Inhibitor of JAK3/TEC-Family (2023)
- All other candidates still in clinical studies:
  - Deuruxolitinib inhibition via JAK1 und JAK2
  - Jaktinib broad spectrum-JAKi
  - SHR0302 highly selective JAK1-Inhibitor

Cytokines with possible implication in AA pathogenesis in **bold**

Th1	Th2	Th9/ IL-9	Th17/ IL-23

Alopecia areata – The Future .....

- Further „small molecules“ for targeted therapies
- Clinical studies for treatment of alopecia areata in children and adolescents using JAK inhibitors

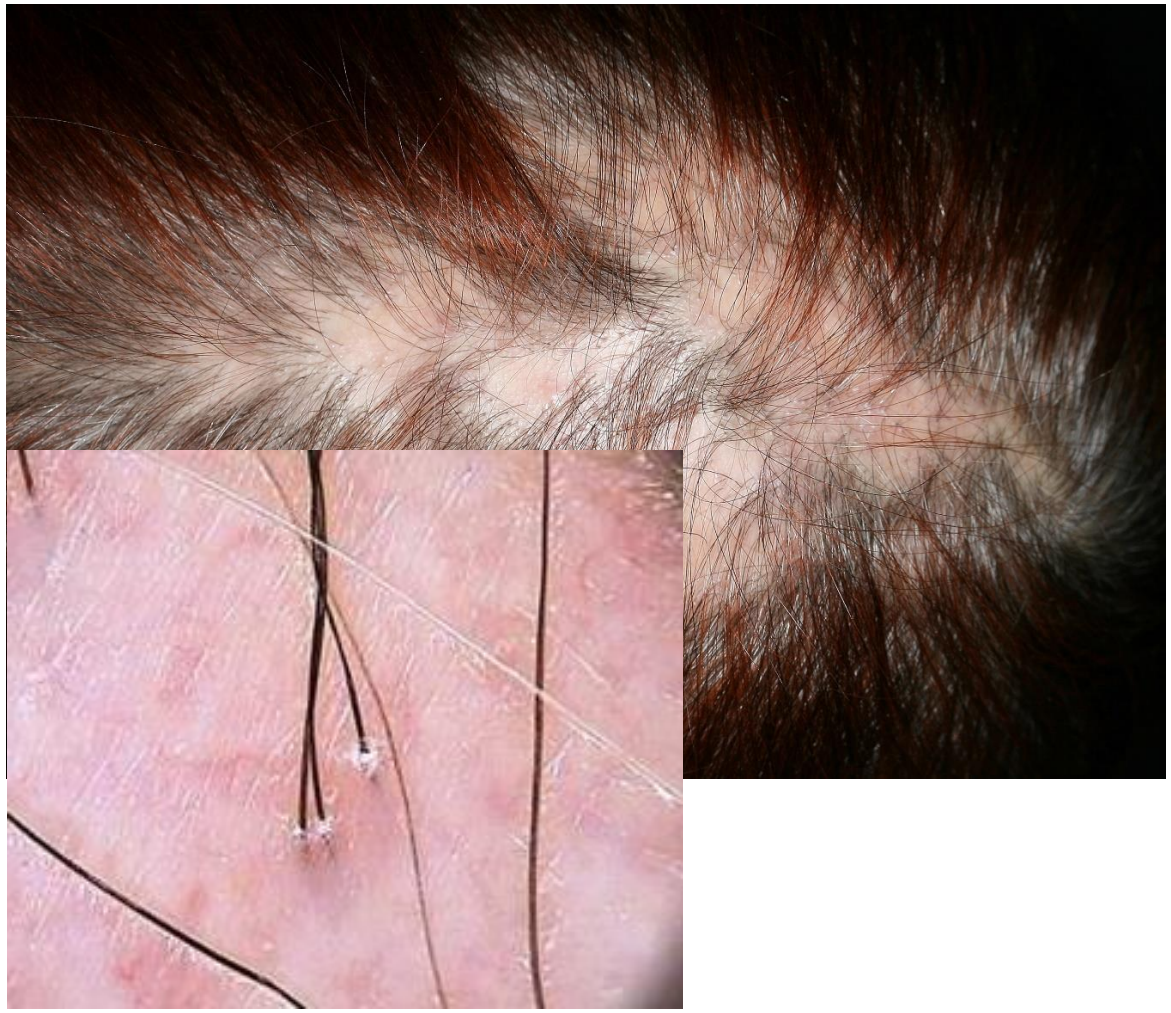
Alopecia areata – Opening of a new treatment landscape

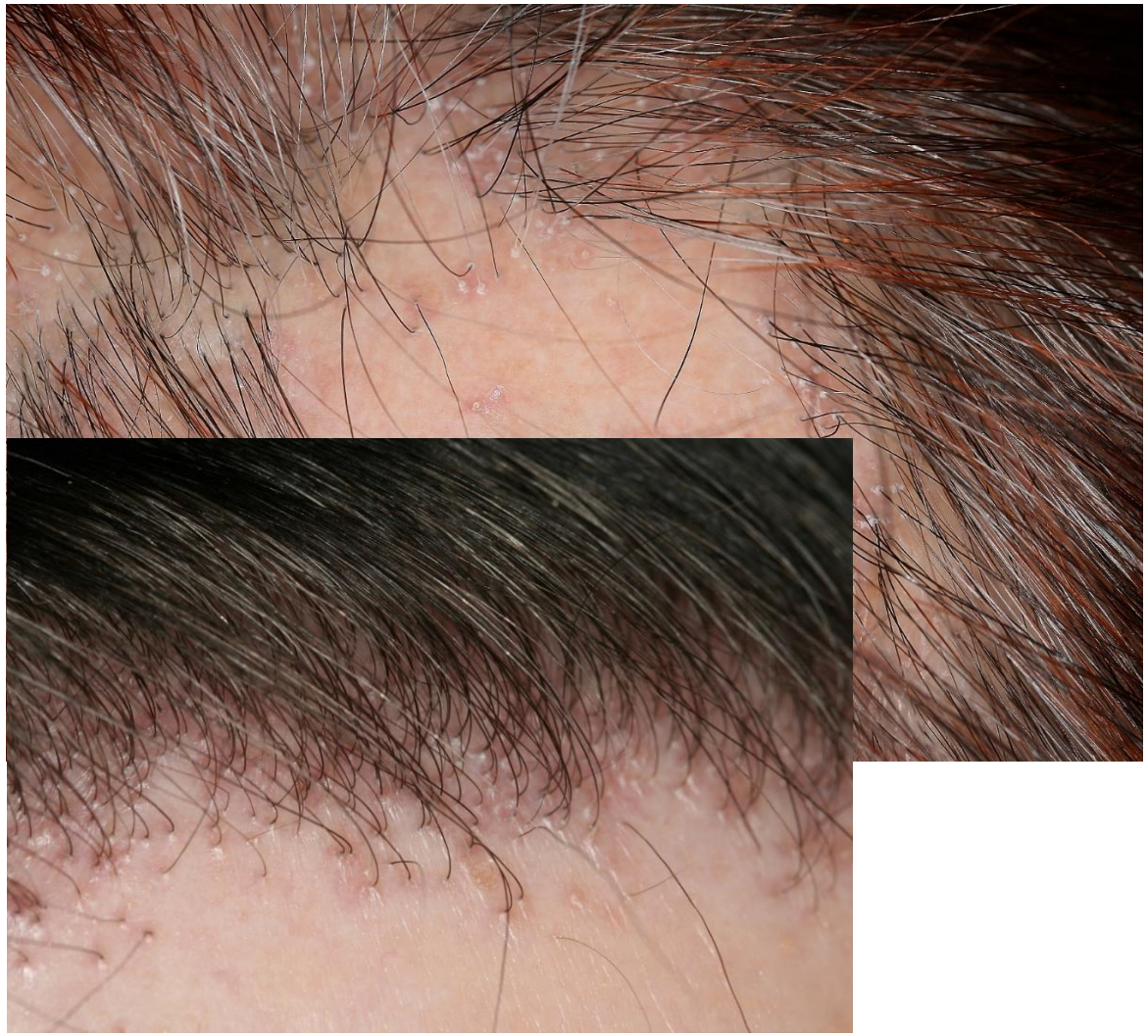
- High emotional burden and high demand from patients
- New understanding of pathogenesis and signaling
- JAK-inhibitors:
  first targeted effective therapy for management of alopecia areata

Alopecia Hair Diseases

Scarring alopecia or permanent hair loss

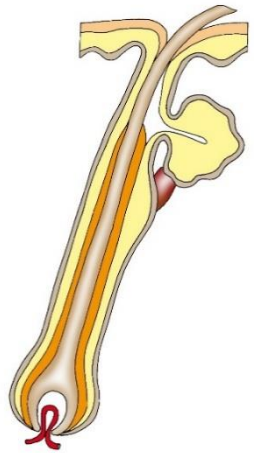
„Scales“ or „Perifollicular Keratosis“?

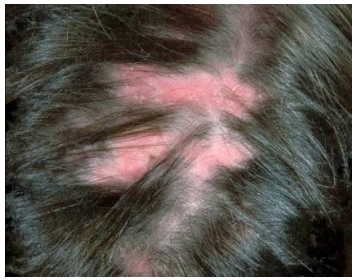


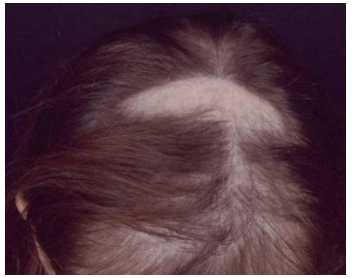


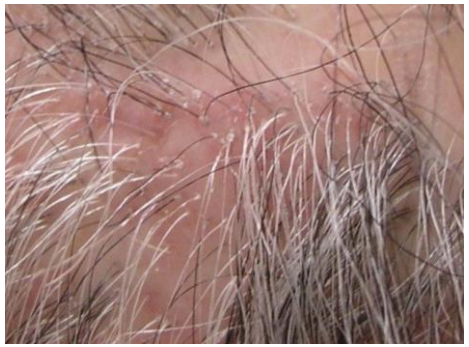
Scarring Alopecia

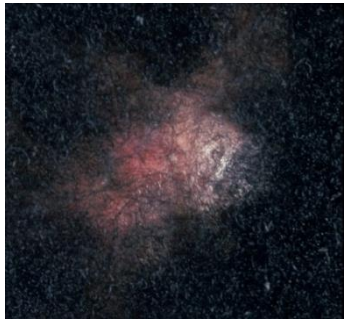
Inflammatory infiltrate	Diagnosis
PCA group I Lymphocytic infiltrate	– Discoid lupus erythematosus of the scalp
	– Lichen planopilaris
	– Classic lichen planopilaris
	– Frontal fibrosing alopecia
	– Graham-Little-Piccardi-Lasseur syndrome
	– Pseudopelade of Brocq
	– Central centrifugal cicatricial alopecia
	– Follicular mucinosis
	– Keratosis follicularis spinulosa decalvans
PCA group II Neutrophilic infiltrate	– Folliculitis decalvans
	– Dissecting cellulitis/Perifolliculitis capitis abscedens et suffodiens
PCA group III Mixed-cell infiltrate	– Acne (folliculitis) keloidalis
	– Acne (folliculitis) necrotica
	– Erosive pustular dermatosis of the scalp
PCA group IV Nonspecific infiltrate	– Idiopathic scarring alopecia with inconclusive clinical and histopathological findings
	– End stage of various inflammatory scarring alopecias

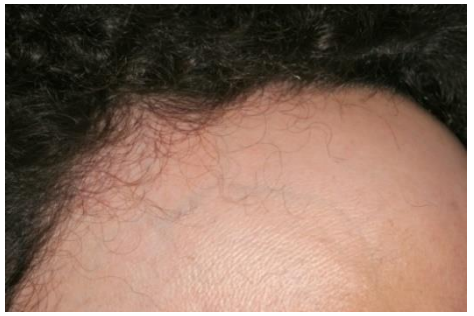


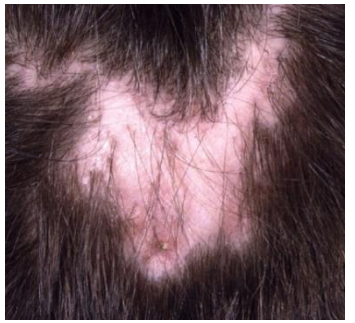












Kanti et al. Cicatricial alopecia. JDDG 2018;16:435-461

„Lichen Planopilaris (LPP) – Classification

Classic (disseminated) type

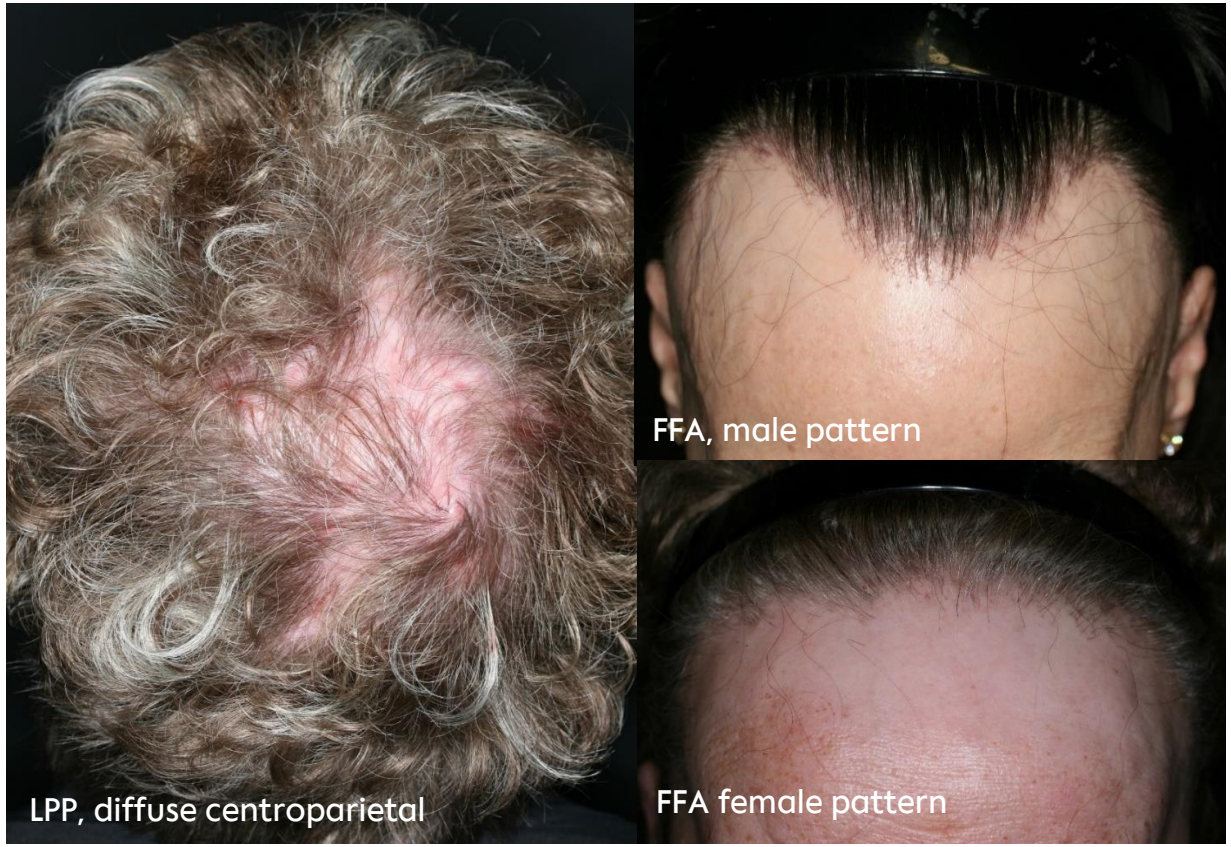
- Isolated disseminated centroparietal scalp manifestations, mainly vertex

Circumscribed type Frontal Fibrosing Alopecia

- Band-like scarring alopecia of the frontal hairline, with frontotemporal recession (male and female pattern type)
- Involvement of eyebrows with loss of ca. 50%
- Facial/body hair may be involved but not as fibrosing alopecia

Graham-Little-Piccardi-Lassueur syndrome

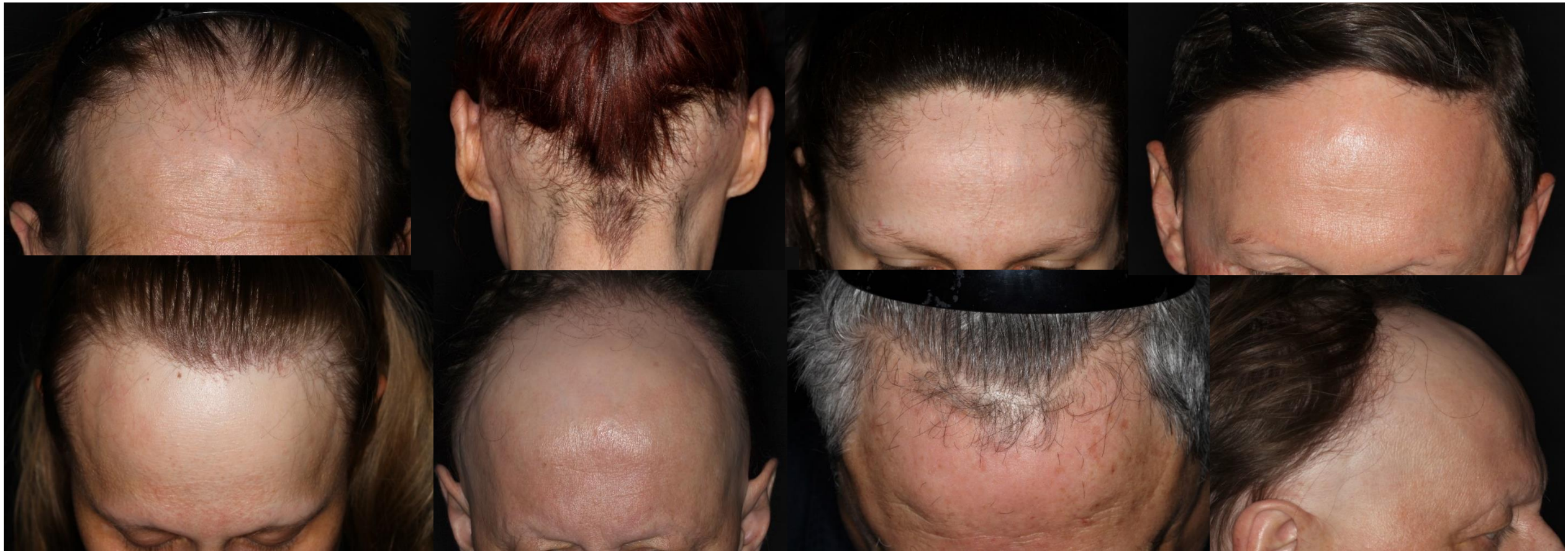
- Scarring hair loss on the scalp with non-scarring body hair follicle involvement, follicular papules on trunk and extremities



Kanti et al. Cicatricial alopecia. JDDG 2018;16:435-461

Frontal Fibrosing Alopecia (FFA)

- First cases reported in 1994 by the American Dermatologist Kossard in post-menopausal women with frontal bandlike scarring alopecia



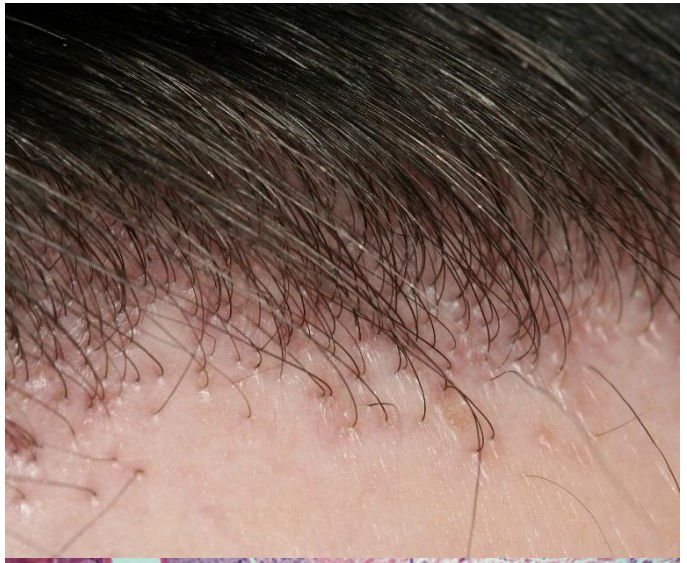
Kossard S. Postmenopausal Frontal Fibrosing Alopecia: Scarring Alopecia in a Pattern Distribution. Arch Dermatol 1994;130:770-774;

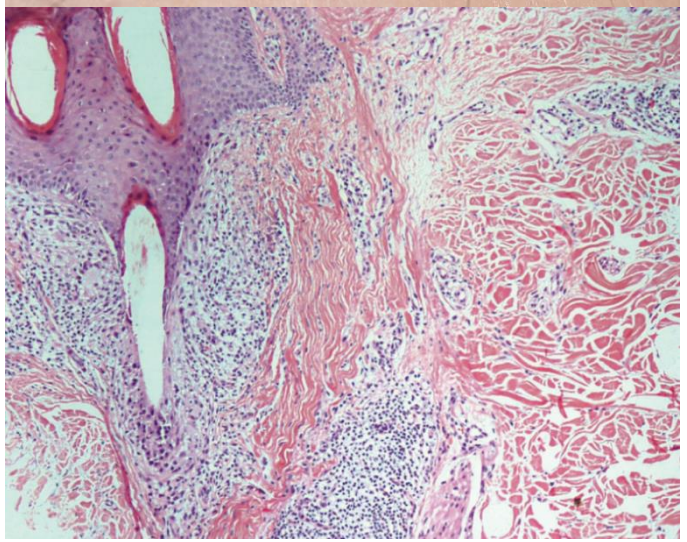
What is causing FFA – How to manage the patient with FFA?

Etiology – Pathogenesis – Pillar for therapeutic approach

1. Inflammation

- Characteristic perifollicular, lymphocytic inflammatory reaction as in LPP (bulge region)
- Etiopathogenesis still unknown but recent research suggests
  - Inflammation-induced hair follicle (HF) stem cell damage
  - Immune privilege collapse of the HF bulge region





Therapeutic approach

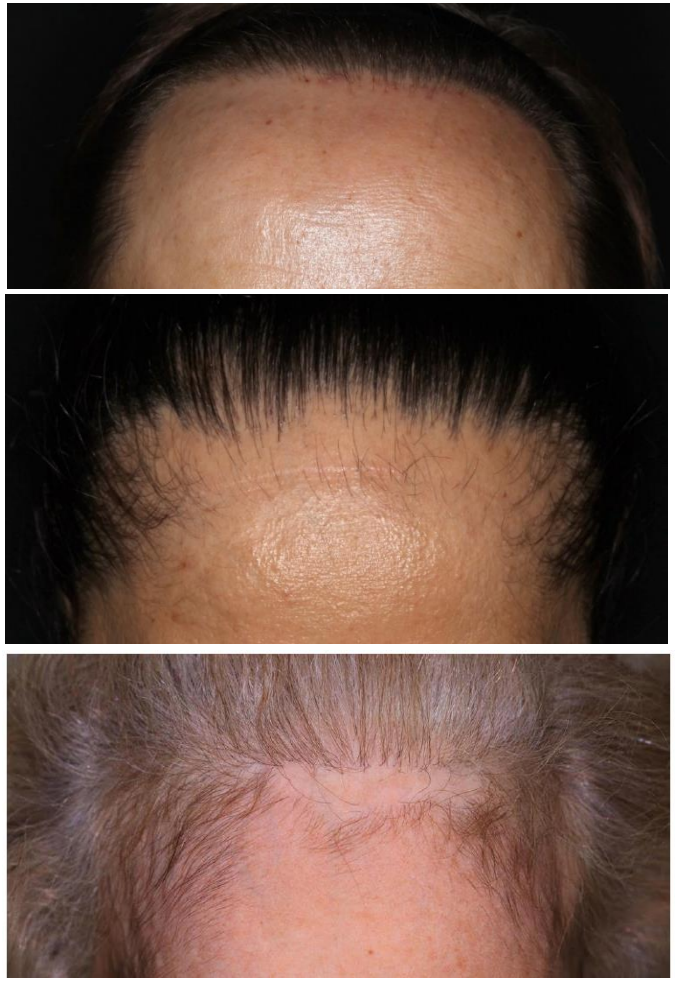
- Immune suppression or immune modulation (corticosteroids, hydroxychloroquine, calcineurin inhibitors)

What is causing FFA – How to manage the patient with FFA?

Further concepts for etiology – Pillar for therapeutic approach

2. Inflammation – Immune signaling

- FFA lesional and even nonlesional scalp show robust immune activation, CD8+ cytotoxic T cells juxtaposed to follicular stem cells, increased IFN-γ production and JAK/signal transducers and activators of JAK/STAT signalling
- Thus FFA may result from T helper 1/JAK-STAT-mediated follicular damage and concomitant fibrosis.
- Early therapeutic targeting of this pathway may have potential to prevent disease progression



Therapeutic approach

- Janus kinase inhibition for treatment of refractory FFA

Del Duca et al. Frontal fibrosing alopecia shows robust T helper 1 and Janus kinase 3 skewing. Br J Dermatol 2020; Dec;183(6):1083-1093.

What is causing FFA – How to manage the patient with FFA?

Etiology – Pathogenesis – Pillar for therapeutic approach

3. Genetic Susceptibility with xenobiotic-processing enzyme genetic defect identified

4. Hormonal link
   - 5α-reductase inhibitors help to stabilize condition
   - Primary portions of the scalp involved common to pattern hair loss
     „Fibrosing alopecia in a pattern distribution“

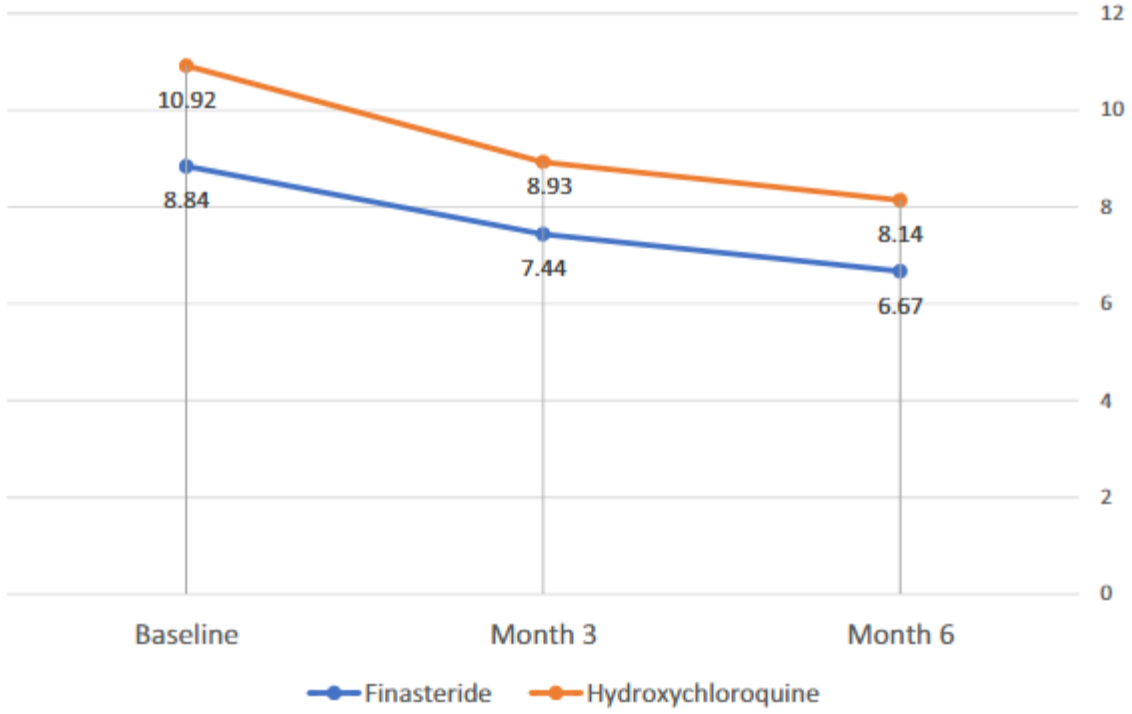
5. Cosmetic products and UV-screens
   - Implication of facial or hair products especially those containing sunscreens, still controversially discussed
   - Link between Linalool sensitisation: high prevalence of relevant contact allergens (gallates, fragrance mixes, linolool) in patients with LPP/FFA

Tziotzios et al. Genome-wide association study in frontal fibrosing alopecia identifies four susceptibility loci including HLA-B*07:02. Nature communications 2019;10:1150
Rayinda et al. Shared Genetic Risk Variants in Both Male and Female Frontal Fibrosing Alopecia. J Invest Dermatol (2023), in press
Maghfour et al. The association between frontal fibrosing alopecia, sunscreen, and moisturizers: A systematic review and meta-analysis. J Am Acad Dermatol 2022;87:395-396
Kam et al. Frontal fibrosing alopecia and personal care product use: a systematic review and meta-analysis. Arch Dermatol Res 2023;315:2313–2331

Frontal Fibrosing Alopecia (FFA) – Inflammation and 5a-reductase inhibitors

Finasteride and Hydroxychloroquine

Frontal Fibrosing Alopecia Severity Scores (FFASS) after 1, 3, and 6 months of treatment



Both finasteride and hydroxychloroquine are equally effective, safe, and well-tolerable for treating FFA patients.

Saber et al. Clinical effectiveness of finasteride versus hydroxychloroquine in the treatment of frontal fibrosing alopecia: A randomized controlled tria J Cosmet Dermatol. 2023;00:1–9

Frontal Fibrosing Alopecia (FFA) – Current Therapeutic Recommendations

First line treatment

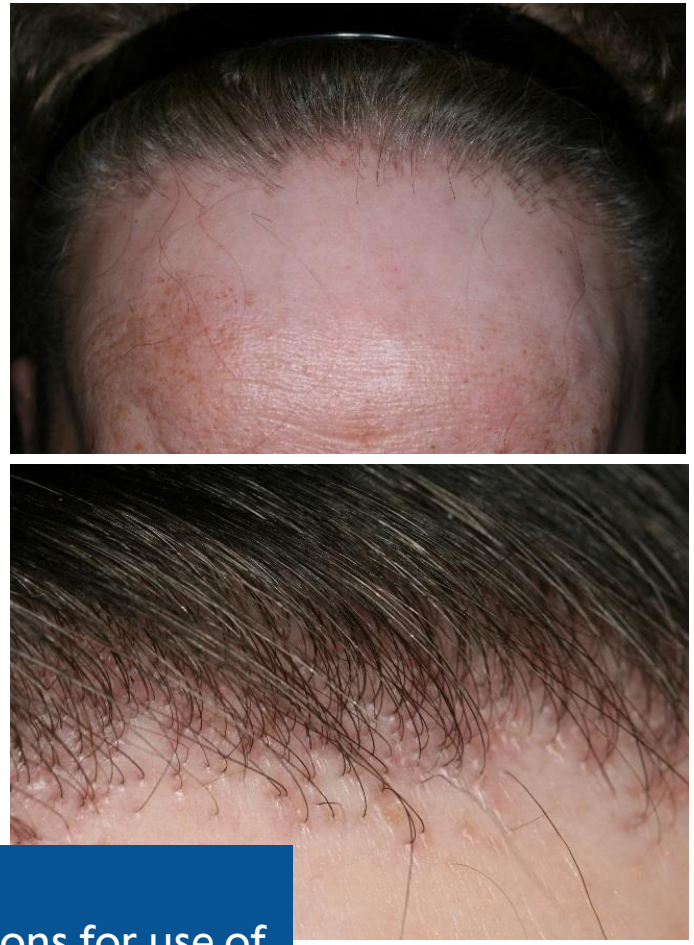
- Topical corticosteroid solution or foam application
- Triamcinolon-injections in the active border

Second line treatment (off label)

- Hydroxychloroquin (2 x 200 mg/day) 6-9 months
- Oral cortison pulse therapy alone or in combination
- Finasterid 2,5 mg/d in combination with minoxidil solution or Dutasterid 0,5 mg/d

Third line treatment (off label)

- Mycophenolatmofetil 2 x1 g/day



- Therapeutic recommendations, symptom-orientiated, anti-inflammatory (off label)
- Need for randomised, controlled studies, to provide evidence based recommendations for use of immunosuppressive, antiandrogen therapies and innovative approaches1

Blume-Peytavi et al. Frontal fibrosing alopecia Hautarzt 2022;73:344-352

3

Take home messages

Alopecia and Hair Diseases – Take home messages

Androgenetic alopecia – Pattern hair loss

- A genetic trait with shortening of hair cycle and miniaturisation of the hair follicle
- Therapeutic management with pharmacologic treatments to prolong hair growth

Alopecia areata

- New understanding of pathogenesis and signaling
- JAK-inhibitors: first targeted effective therapy for management of alopecia areata

Lichen planopilaris and Frontal fibrosing alopecia

- Topical and / or systemic immune suppressive – immune modulatory approach
- Further research for understanding pathogenesis to develop preventive or targeted approach

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