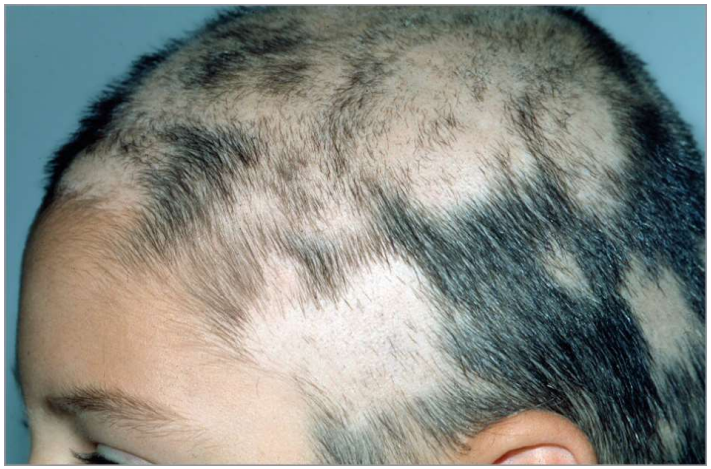
Ursachen, Therapie und Ausblick in die Zukunft



Armina Schulte Oberärztin Dermatologie,
Fachklinik Bad Bentheim

Fachklinik
Bad Bentheim

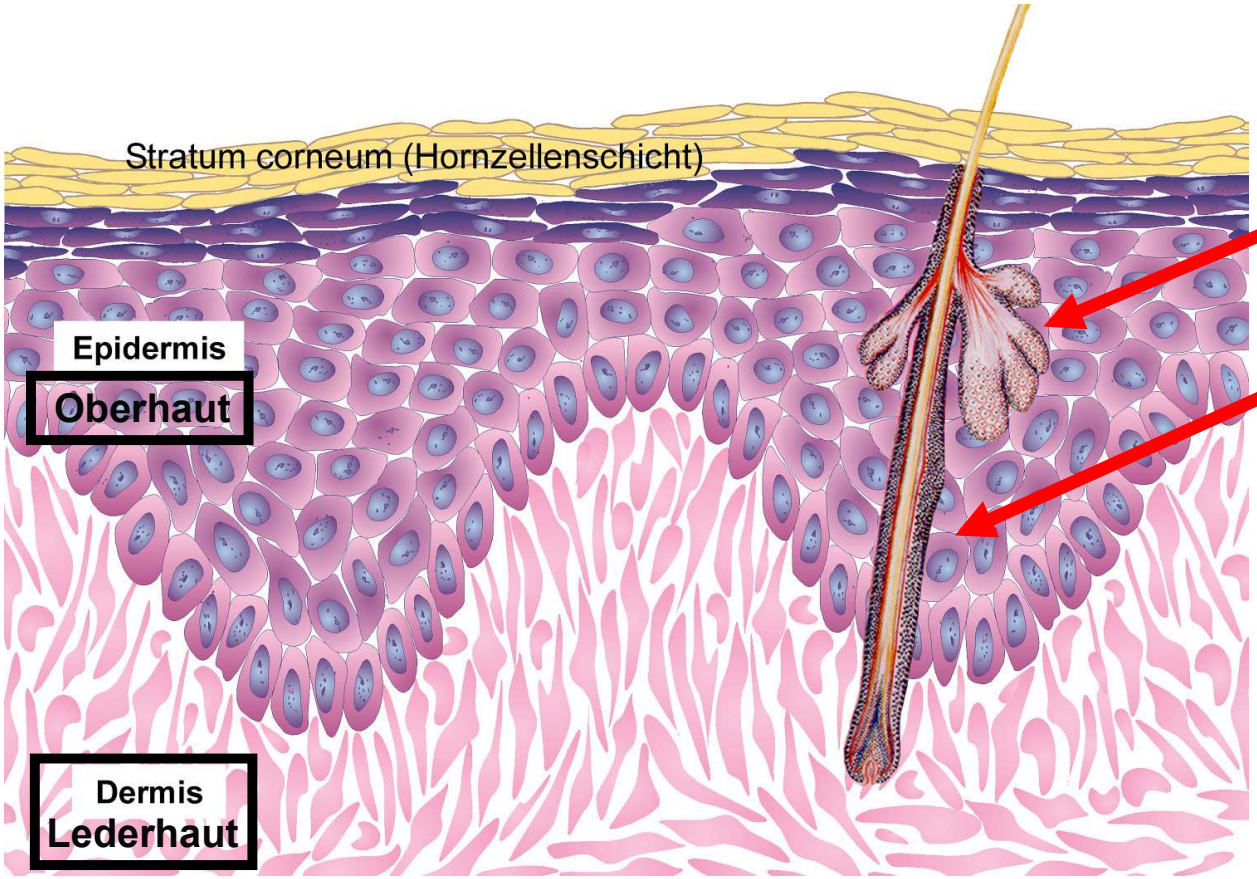
Rheumatologie · Dermatologie
Orthopädie · Kardiologie

Alopecia areata

- Einer der häufigsten Formen von Haarverlust, die ca. 1-2% der Bevölkerung betrifft
- Ursache multifaktoriell: Dies bedeutet, dass sowohl genetische als auch Umweltfaktoren eine Rolle bei der Entstehung spielen.
- Bisherige Untersuchungen geben starke Hinweise auf eine Autoimmun-Ursache (d.h. überschießendes Immunsystem, das gegen den eigenen Körper gerichtet ist)
- Diese Überaktivierung tritt aber nur bei Patienten auf, die spezielle Gene haben, die bedingen, dass das Immunsystem sich zu leicht aktivieren lässt
- AA wird mit anderen Autoimmunerkrankungen (zum Beispiel Schilddrüsenerkrankungen, Vitiligo, Lupus erythematodes), Neurodermitis, Stress und psychiatrischen Störungen (zum Beispiel Angstzustände, Depressionen) in Verbindung gebracht.

Unsere Haut

Oberhaut:
- Barriere
- wasserdicht

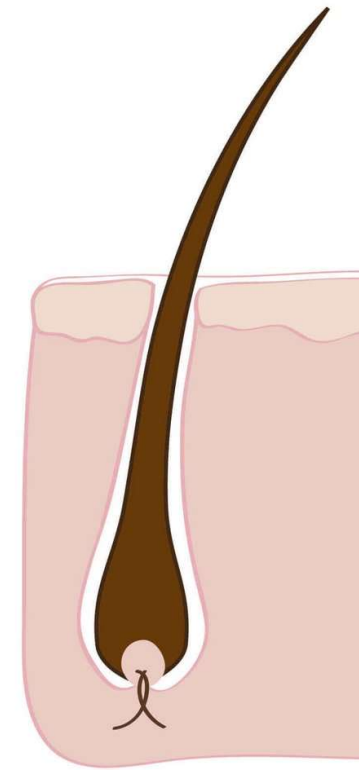


Talgdrüse

Haar mit Haarwurzel

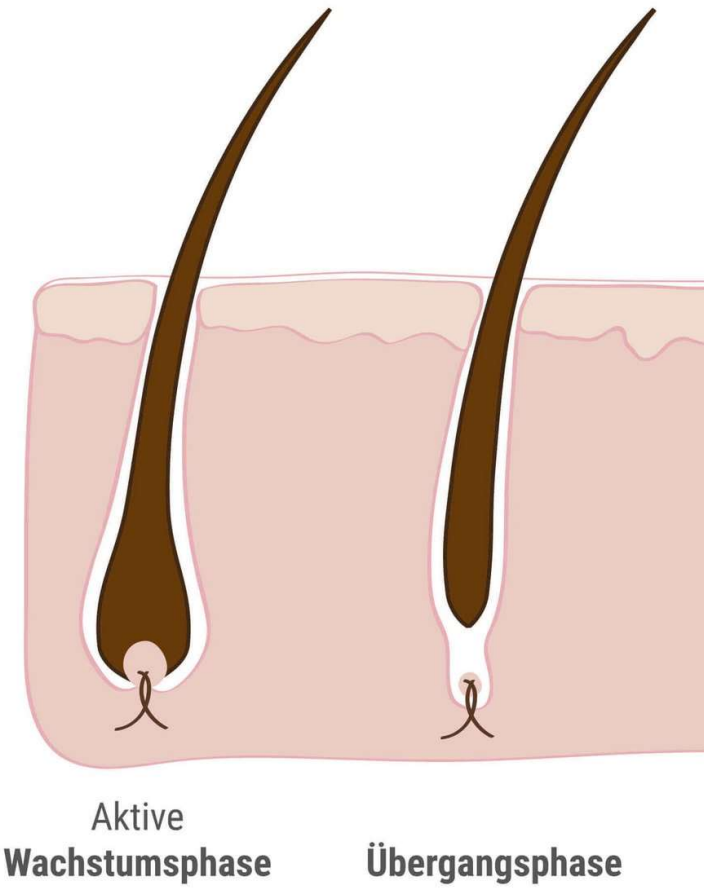
Lederhaut:
- Festigkeit
- Elastizität

Das Leben eines Haares

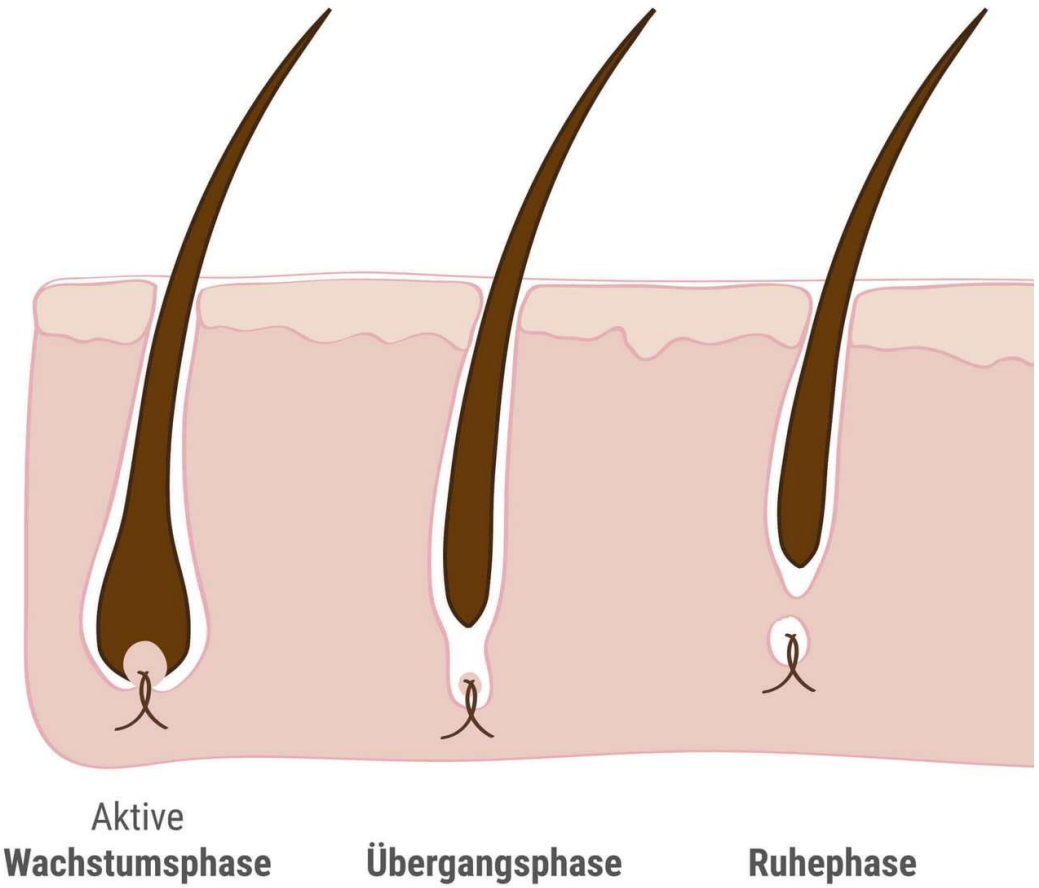


Aktive
Wachstumsphase

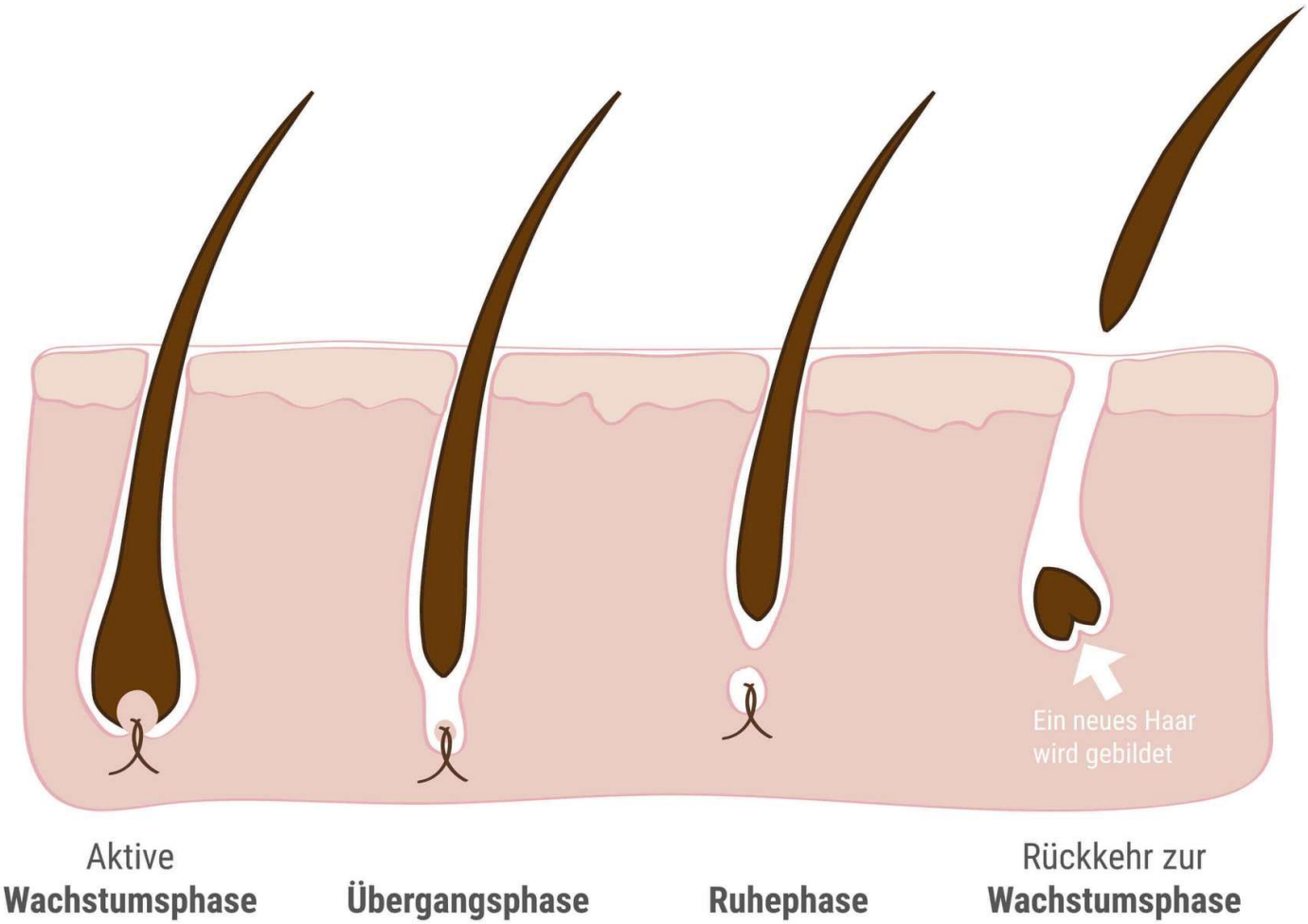
Das Leben eines Haares



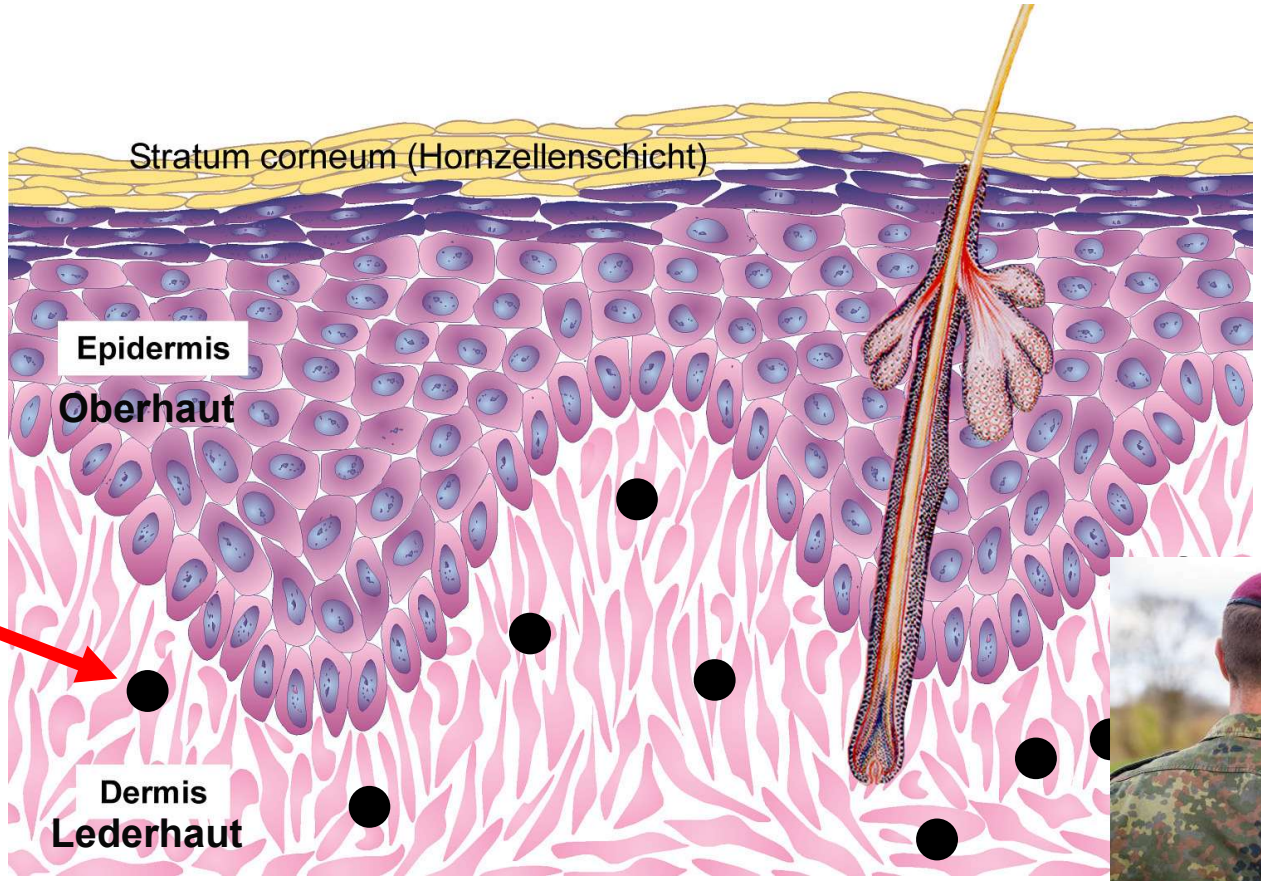
Das Leben eines Haares



Das Leben eines Haares

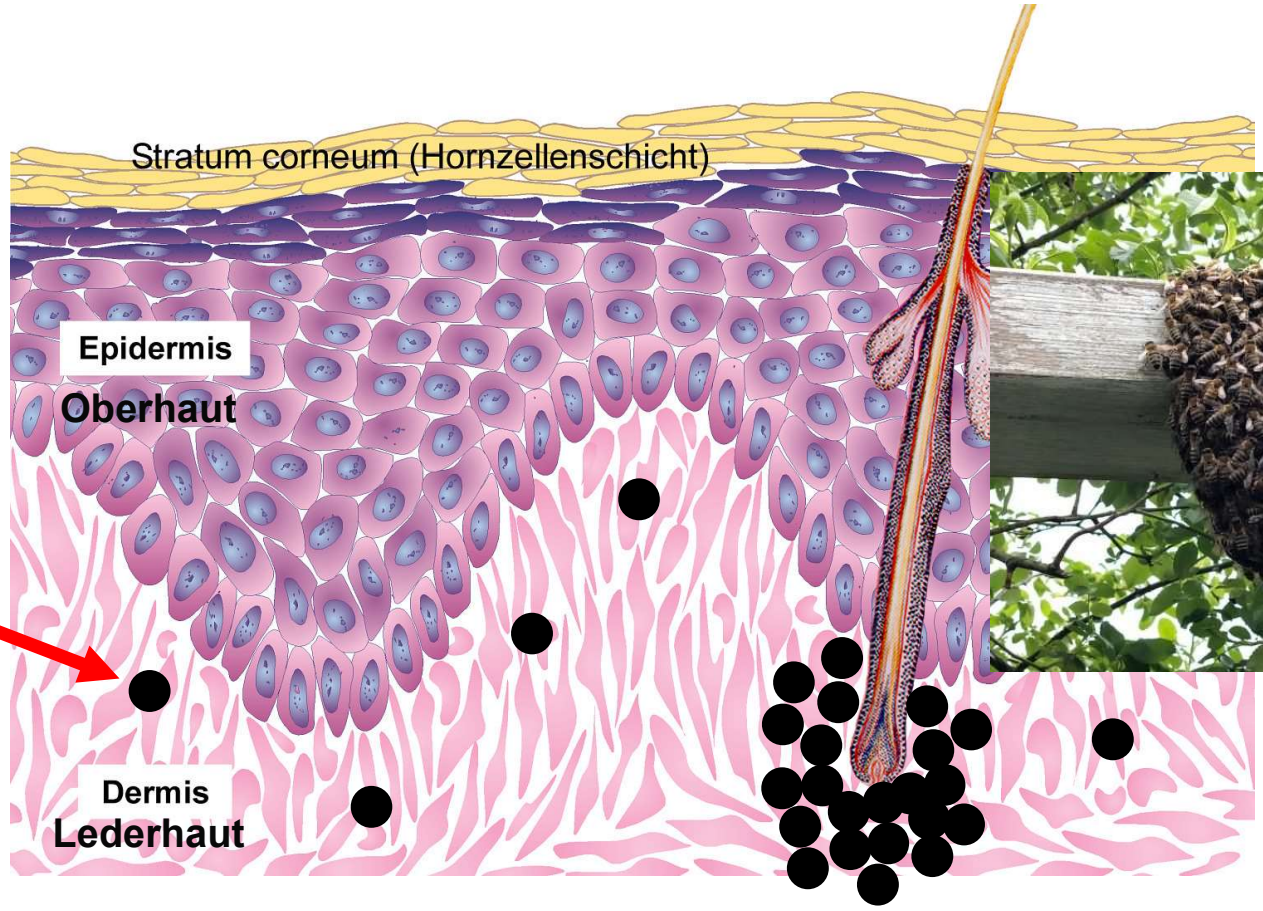


Unsere Haut



Immunzellen

Alopecia areata



Immunzellen

überaktivierte Immunzellen

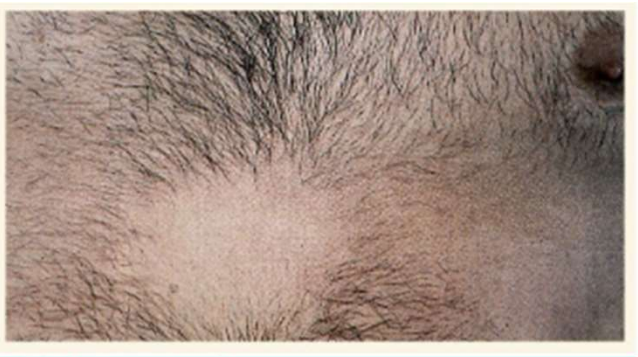


Abb. 1: Alopezia areata prästernal

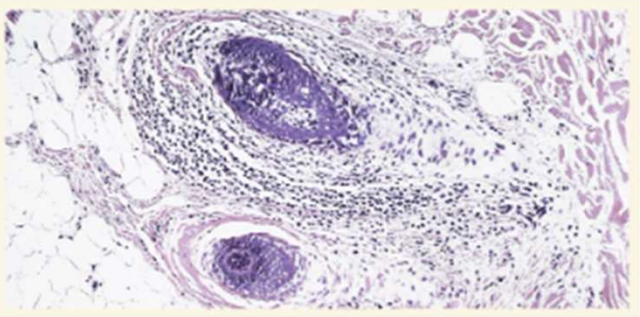
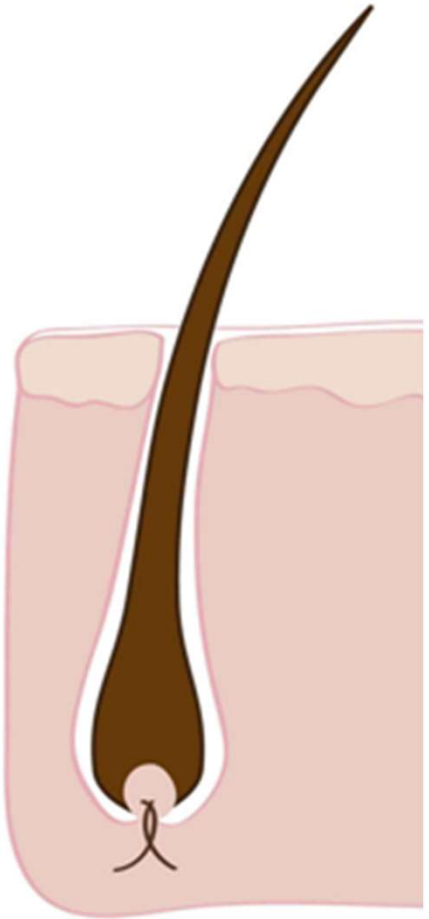
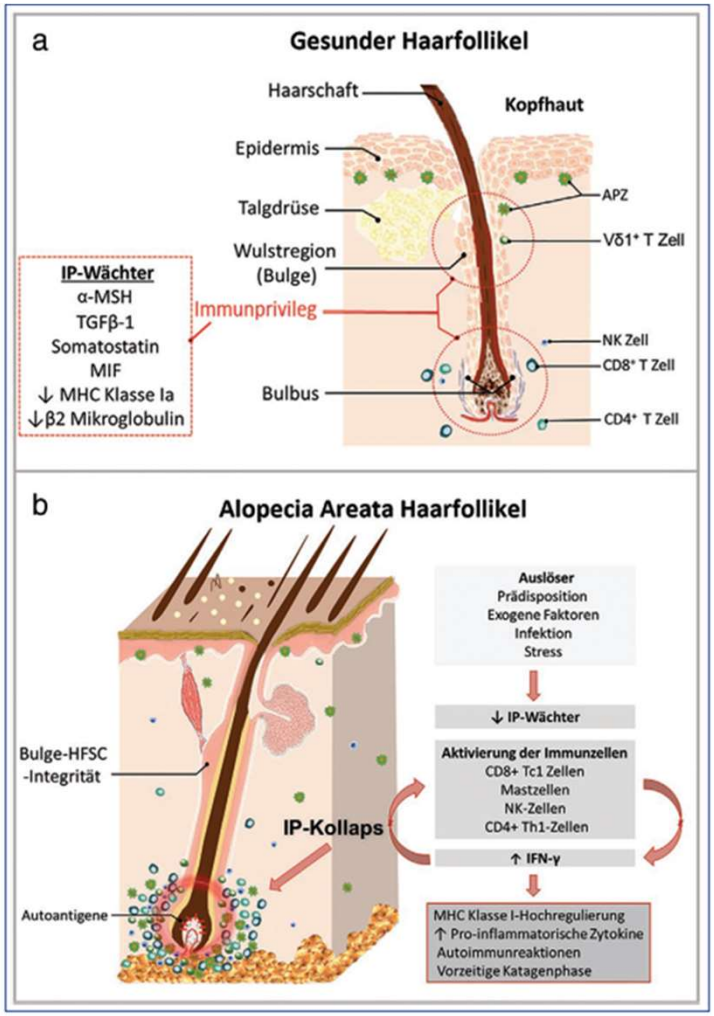


Abb. 2: Lymphohistiozytäres Entzündungsinfiltrat um den Haarfollikel

Der Kollaps des Haarfollikels spielt eine entscheidende Rolle in der Entstehung der Alopecia areata.





J Deutsche Derma Gesell 2022 Lintzeri

Genetik?

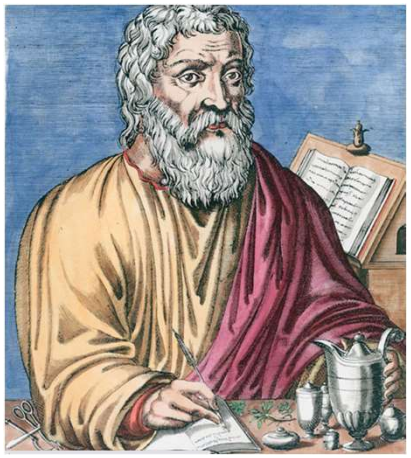
- Bei der Alopecia areata wird von einer genetisch komplexen Vererbung mit einer Vielzahl krankheitserregender Gene ausgegangen.
- Das Erkrankungsrisiko für Verwandte ersten Grades eines Betroffenen beträgt ca. 7% für Geschwister, für Eltern knapp 8% und für Kinder knapp 6%. Das Risiko für zweitgradig Verwandte entspricht dem der Allgemeinbevölkerung und liegt bei 1-2%.
- Bislang wurden insgesamt 10 verschiedene Gene identifiziert. Besonders hervorzuheben ist hierbei die HLA-Region auf dem kurzen Arm von Chromosom 6. (HLA Gen zeigt eine enge Assoziation zu Autoimmunerkrankungen).

J Invest Dermatol 2011, 131: 1169-1172

Twins with Alopecia Areata Both Develop Thyroid Problems

Schipani et al. Dermatol Pract Concept. 2019 Jul; 9(3): 241–243.

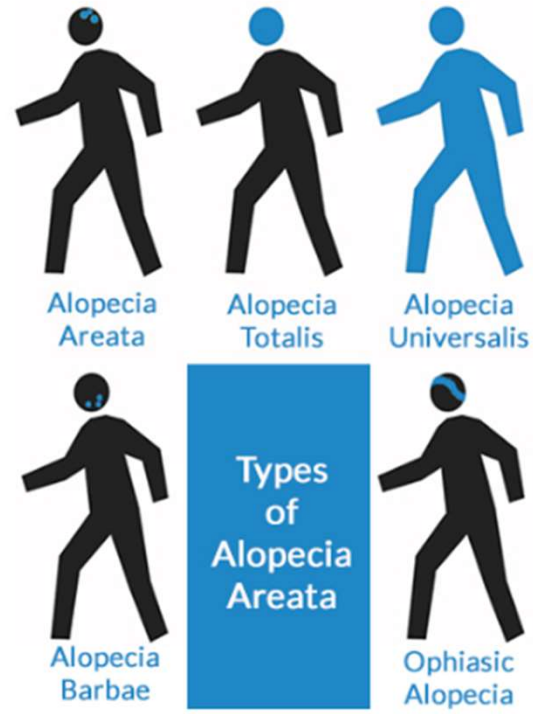
Geschichte



Hippokrates von Kos, einer der berühmtesten Ärzte der Antike, 400 Jahre v.Chr.
In seinem Werk ‘‘de aflectionibus‘‘ erwähnte er die Alopecia areata.

Prof. Dr. med. Gerhard Lutz Akt Dermatol 2017; 43: 108

Alopecia areata Formen

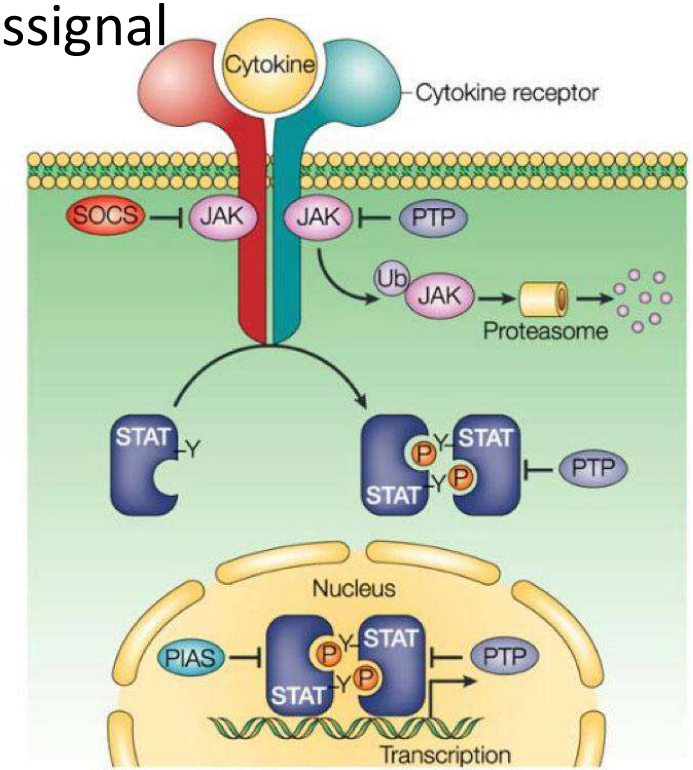


Areas affected by hair loss shown in blue

Wie werden Immunzellen aktiviert?

Wie kommt das Signal vom Zytokin in den Zellkern?

Entzündungssignal

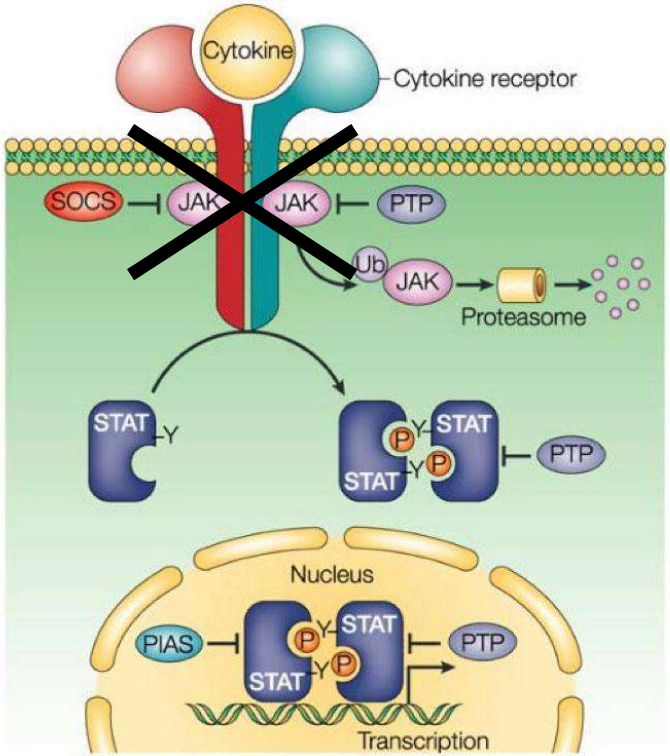


Zelle

- JAK1
- JAK2
- JAK3
- Tyk2

https://www.trillium.de/zeitschriften/trillium-immunologie/archiv/heft-1/2021-signalwege/mutationen-im-jak-stat-signalweg-und-ihre-klinischen-konsequenzen.html

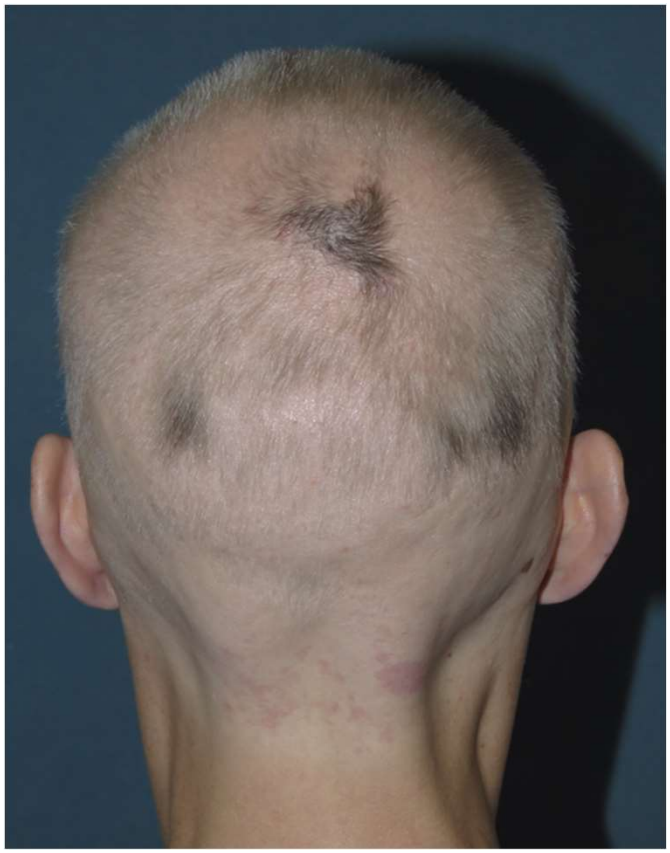
Idee: Aktivierung der Immunzellen blockieren

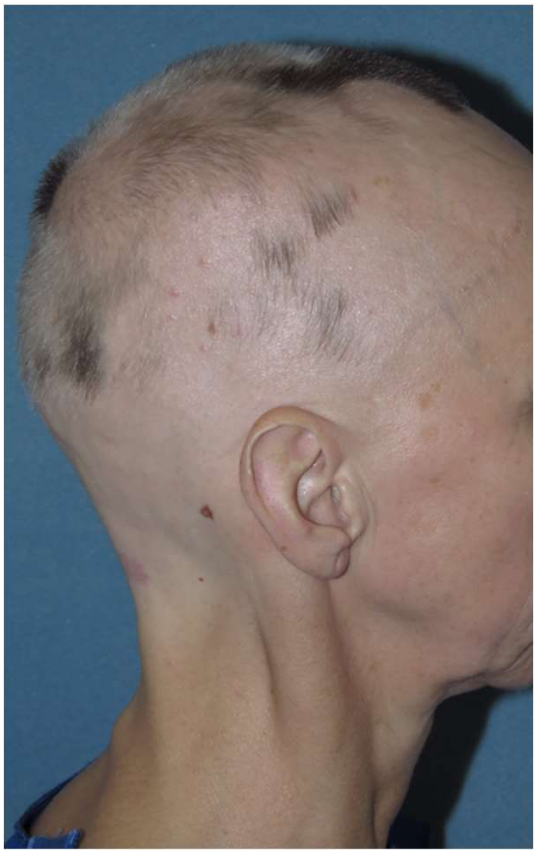


JAK Inhibitoren

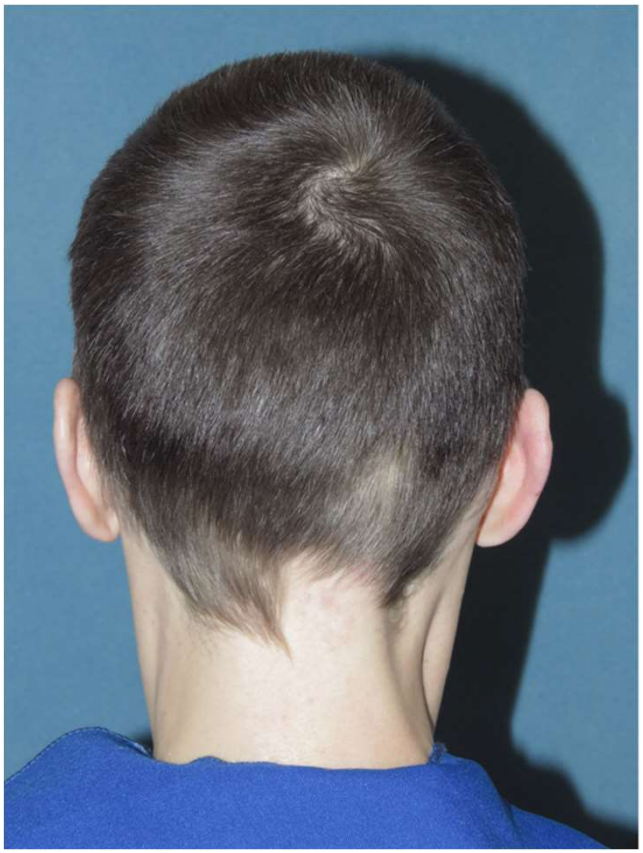
- **Tofacitinib** (JAK3, JAK1 > JAK2)
  - Psoriasis-Arthritis
  - Rheumatoide Arthritis
  - Colitis ulcerosa
- **Baricitinib** (JAK1, JAK2)
  - Rheumatoide Arthritis
  - Atopisches Ekzem
- **Upadacitinib** (JAK1, JAK3)
  - Psoriasis-Arthritis
  - Rheumatoide Arthritis
  - Atopisches Ekzem
- **Ruxolitinib** (JAK1, JAK2)
  - Myelofibrosis
  - Polycythaemia vera
- **Filgotinib** (JAK1)
  - Rheumatoide Arthritis
  - Colitis ulcerosa
- **Abrocitinib** (JAK1)
  - Atopisches Ekzem

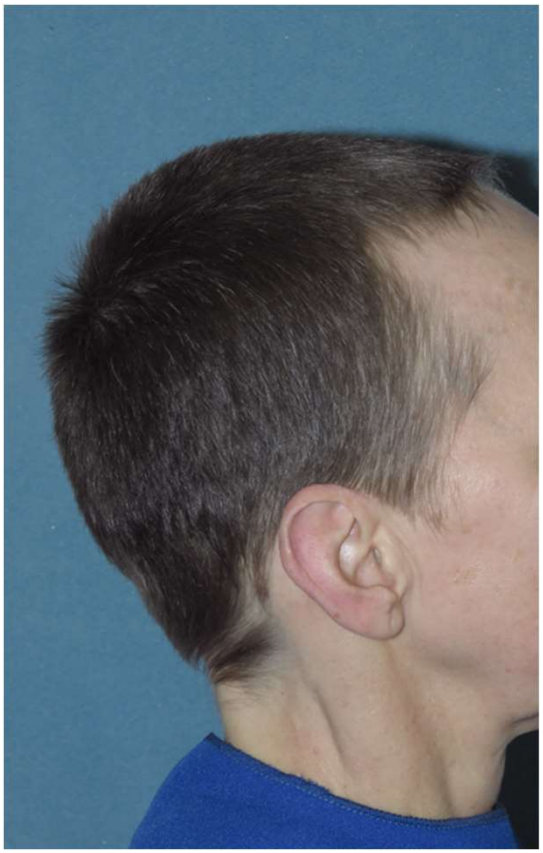
Vor Therapiestart



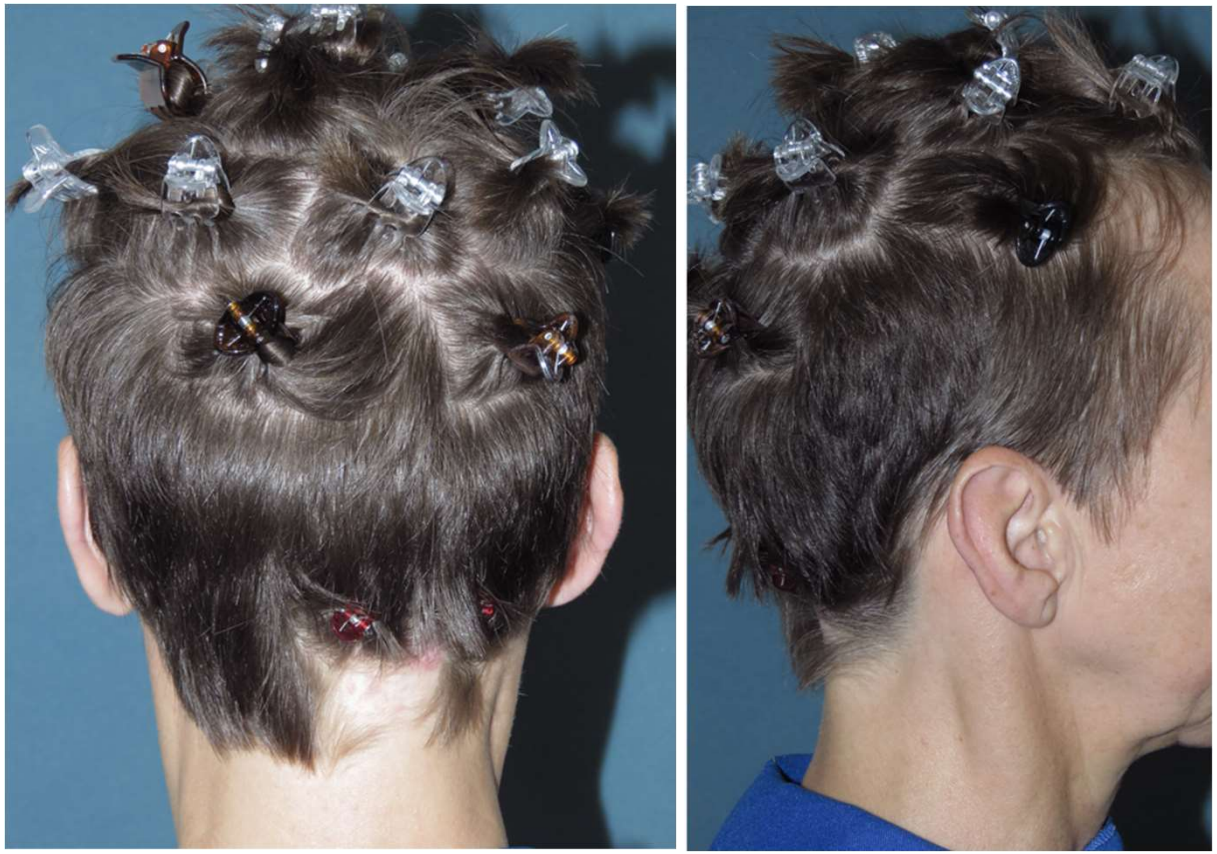


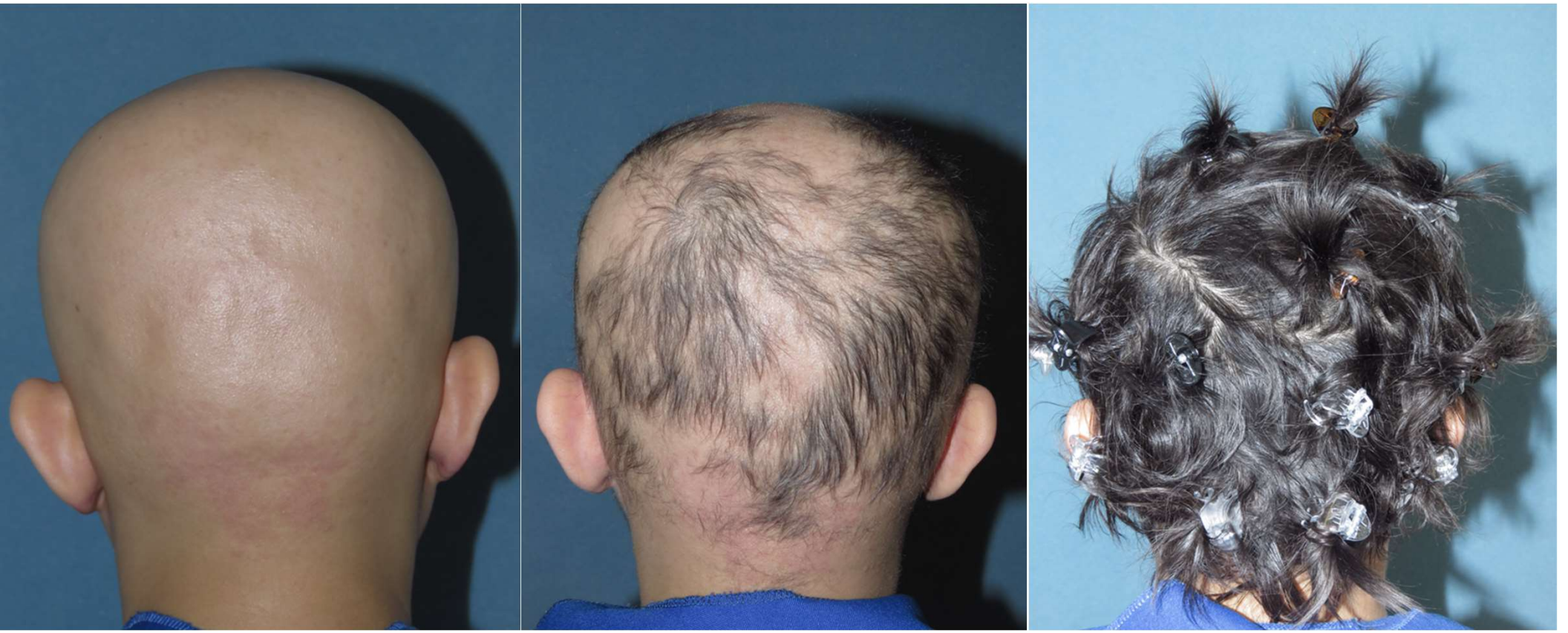
6 Monate später: Therapie mit PF-06651600 (JAK3 Inhibitor)



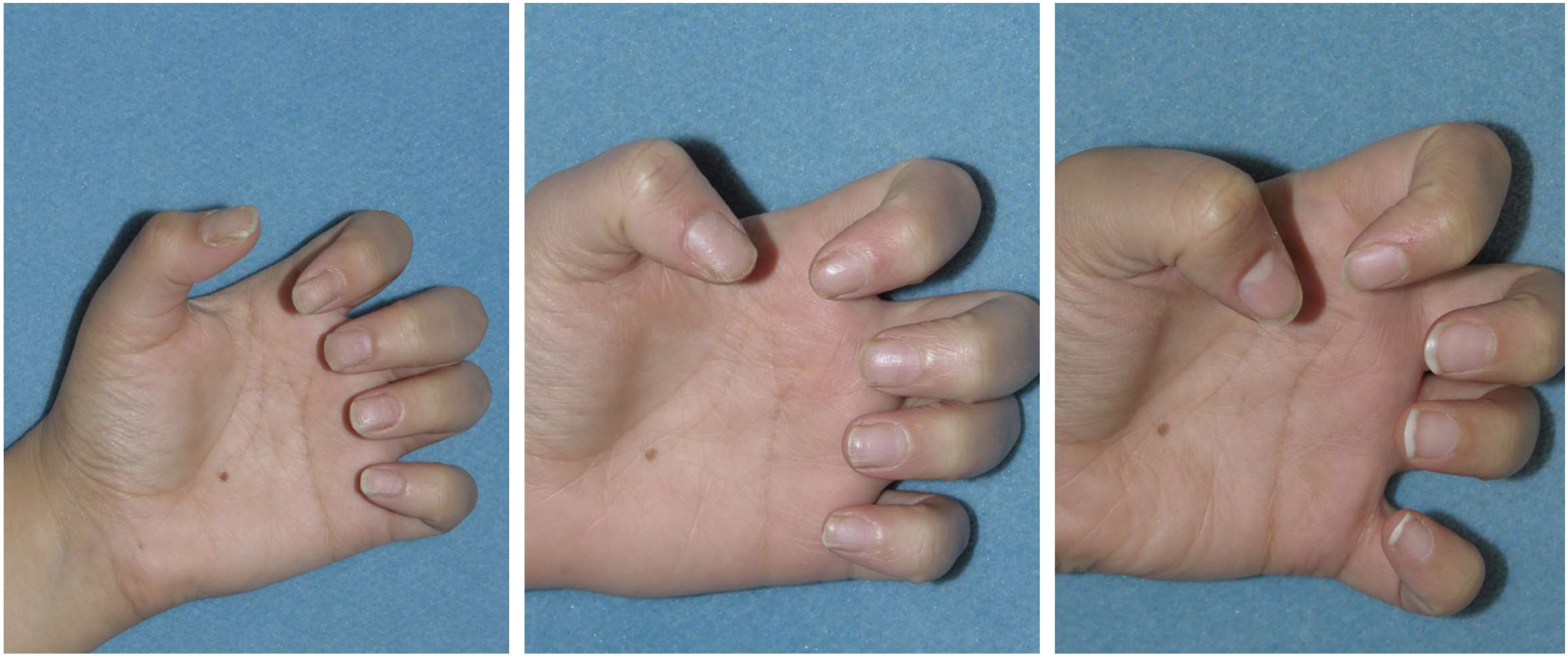


12 Monate





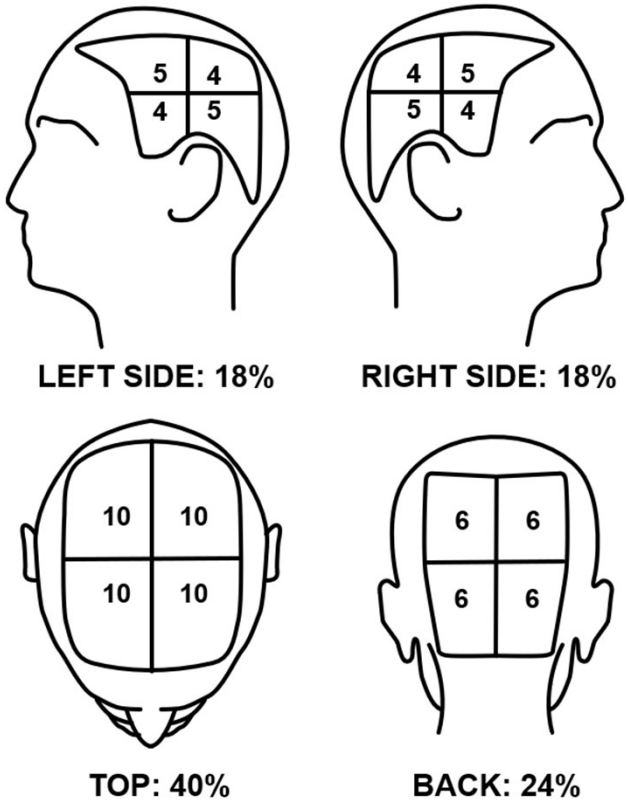
One study of alopecia areata in children observed that 46 percent also had nail abnormalities



Chien Jr. MD PhD, Olympia I Kovich MD Dermatology Online Journal 14 (5): 24

SALT SCORE[1]

- Assess scalp hair loss in each quadrant of the scalp
- The SALT score is a weighted sum of the percent of hair loss in the 4 quadrants of the scalp, ranging from 0 (no hair loss) to 100 (complete hair loss)
- Examples:
  - SALT score 0=no hair loss
  - SALT score 50=50% hair loss
  - SALT score 100=complete hair loss



1. Olsen EA, et al. *J Am Acad Dermatol*. 2004;51:440-447.

SALT=Severity of Alopecia Tool

Alopecia areata

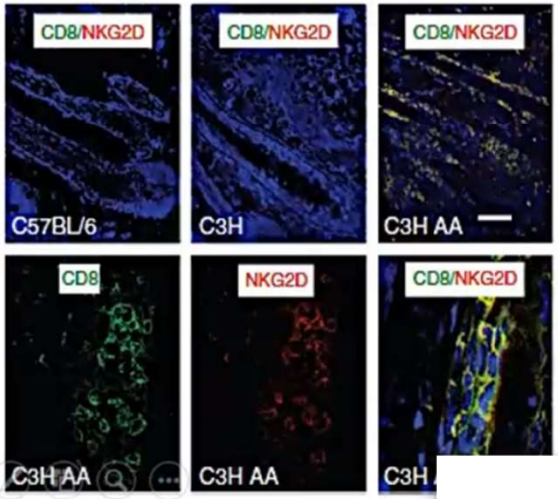
from bench to bedside

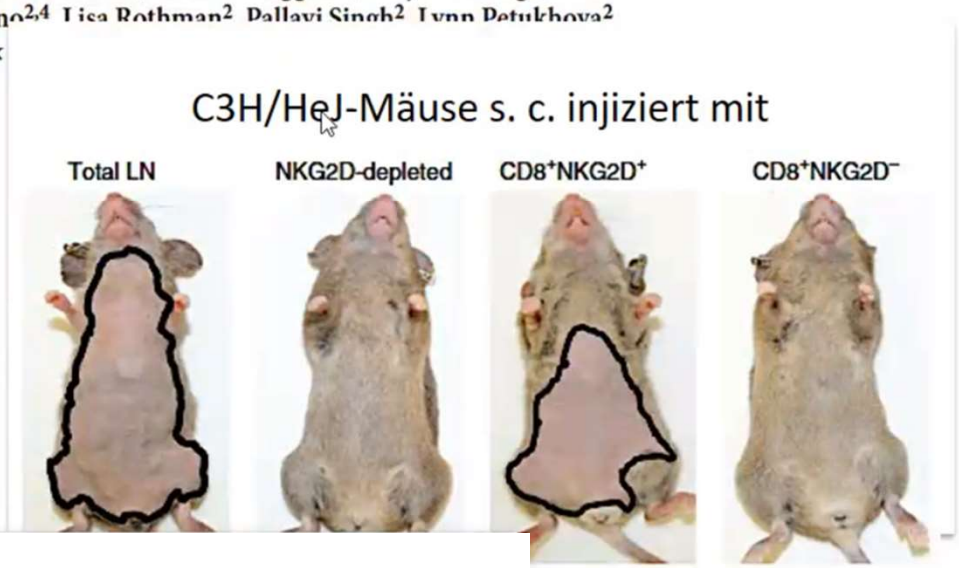
LETTERS

nature medicine September 2014

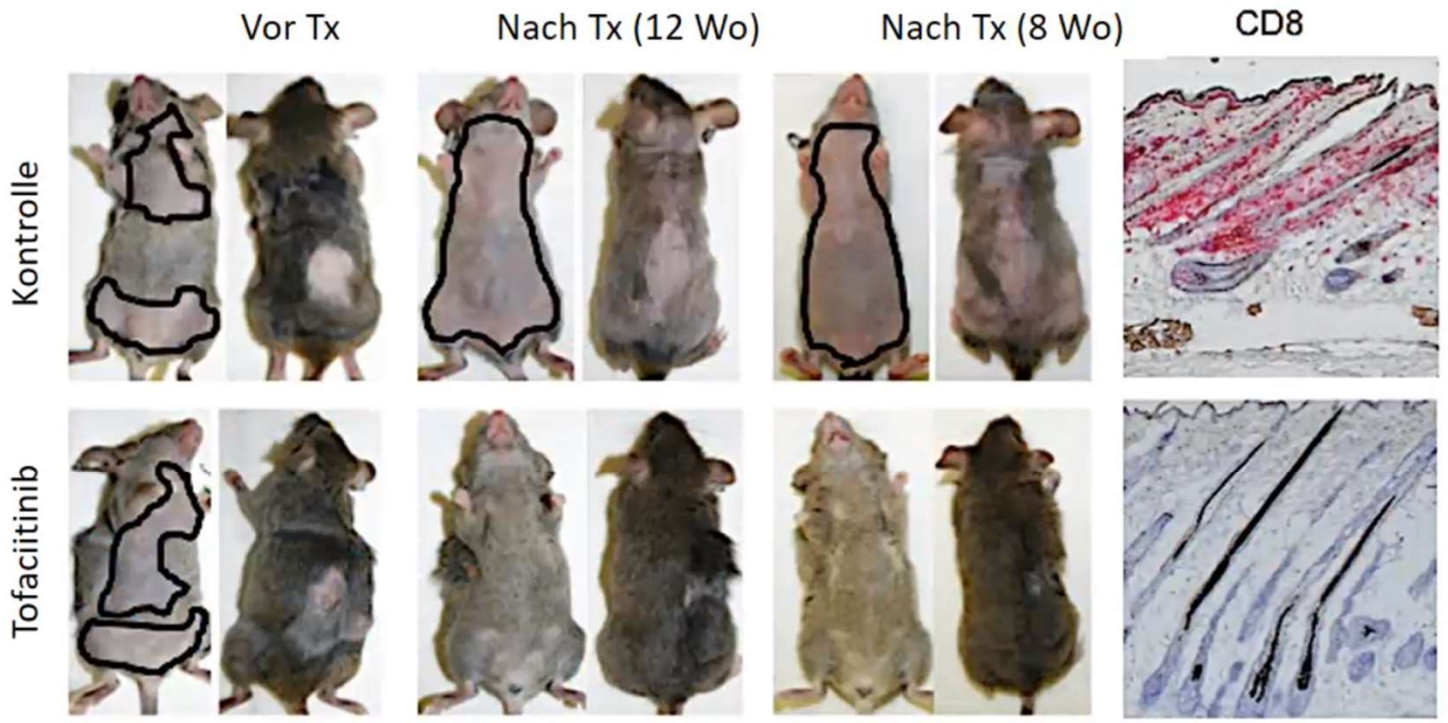
Alopecia areata is driven by cytotoxic T lymphocytes and is reversed by JAK inhibition

Luzhou Xing[1,7], Zhenpeng Dai[2,7], Ali Jabbari[2,7], Jane E Cerise[2,3], Claire A Higgins[2], Weijuan Gong[2], Annemieke de Jong[2], Sivan Harel[2], Gina M DeStefano[2,4], Lisa Rothman[2], Pallavi Singh[2], Lynn Petukhova[2], Julian Mackay-Wiggan[2], Angela M Christiano[2,5,8] &





Systemische Behandlung der Alopecia areata der Maus mit einem JAK1/3-Inhibitor



C3H/HeJ-Mäuse mit lang bestehender A. a. wurden s. c. mit dem JAK1/3-Inhibitor Tofacitinib 15 mg/kg/Tag for 12 Wochen oder mit Vehikel behandelt.

Alopecia areata

Baricitinib

ORIGINAL ARTICLES

Efficacy and safety of the oral Janus kinase inhibitor baricitinib in the treatment of adults with alopecia areata: Phase 2 results from a randomized controlled study

Brett King, MD, PhD,[a] Justin Ko, MD, MBA,[b] Seth Forman, MD,[c] Manabu Ohyama, MD, PhD,[d] Natasha Mesinkovska, MD, PhD,[e] Guanglei Yu, PhD,[f] Jill McCollam, PharmD,[f] Margaret Gamalo, PhD,[g] Jonathan Janes, MB BCh, MRCP,[f] Emily Edson-Heredia, MPH,[f] Katrin Holzwarth, MD, DAS,[f] and Yves Dutronc, MD[f]

New Haven, Connecticut; Stanford, California; Tampa, Florida; Tokyo, Japan; Irvine, California; Indianapolis, Indiana; and Collegeville, Pennsylvania

Background: There are no treatments approved by the Food and Drug Administration for alopecia areata.

Objective: To evaluate the efficacy and safety of baricitinib in patients with ≥50% scalp hair loss in a phase 2 study of adults with alopecia areata (BRAVE-AA1).

Methods: Patients were randomized 1:1:1:1 to receive placebo or baricitinib 1 mg, 2 mg, or 4 mg once daily. Two consecutive interim analyses were performed after all patients completed weeks 12 and 36 or had discontinued treatment prior to these time points. The primary endpoint was the proportion of patients achieving a Severity of Alopecia Tool (SALT) score ≤20 at week 36. Logistic regression was used with nonresponder imputation for missing data.

Results: A total of 110 patients were randomized (placebo, 28; baricitinib 1-mg, 28; 2-mg, 27; 4-mg, 27). The baricitinib 1-mg dose was dropped after the first interim analysis based on lower $SALT_{50}$ response rate. At week 36, the proportion of patients achieving a SALT score of ≤20 was significantly greater in baricitinib 2-mg (33.3%, $P = .016$) and 4-mg (51.9%, $P = .001$) groups versus placebo (3.6%). Baricitinib was well tolerated with no new safety findings.

Limitations: Small sample size limits generalizability of results.

Conclusion: These results support the efficacy and safety of baricitinib in patients with ≥50% scalp hair loss. (J Am Acad Dermatol 2021;85:847-53.)

Key words: AA; alopecia areata; baricitinib; clinician-reported; CTP-543; efficacy; hair loss; JAK; Janus kinase; patient-reported; randomized; ruxolitinib; safety; SALT; tofacitin

- 110 Patienten mit SALT >50%
- 4-armige Studie: Placebo, Baricitinib 1, 2 und 4 mg/die
- Behandlungsdauer 36 Wochen
- Primärer Endpunkt SALT ≤ 20%

Alopecia areata

Baricitinib

ORIGINAL ARTICLES

Efficacy and safety of the oral Janus kinase inhibitor baricitinib in the treatment of adults with alopecia areata: Phase 2 results from a randomized controlled study

Brett King, MD, PhD,[a] Justin Ko, MD, MBA,[b] Seth Forman, MD,[c] Manabu Ohyama, MD, PhD,[d] Natasha Mesinkovska, MD, PhD,[e] Guanglei Yu, PhD,[f] Jill McCollam, PharmD,[f] Margaret Gamalo, PhD,[g] Jonathan Janes, MB BCh, MRCP,[f] Emily Edson-Heredia, MPH,[f] Katrin Holzwarth, MD, DAS,[f] and Yves Dutronc, MD[f]

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Key words: AA; alopecia areata; baricitinib; clinician-reported; CTP-543; efficacy; hair loss; JAK; Janus kinase; patient-reported; randomized; ruxolitinib; safety; SALT; tofacitin

Endpunkt erreicht!
Vs. Placebo und dosisahängig

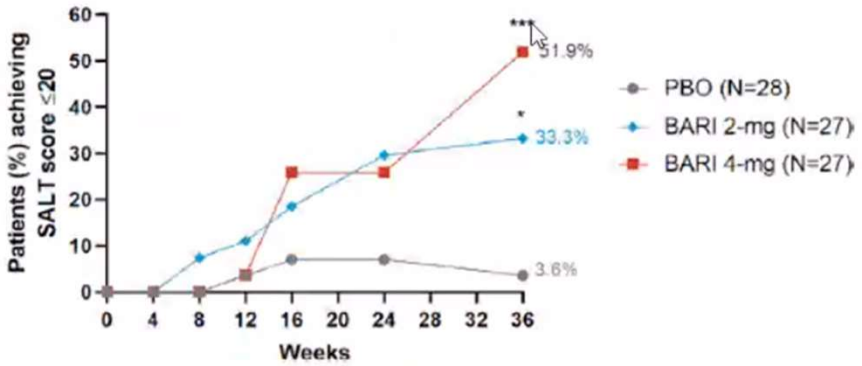
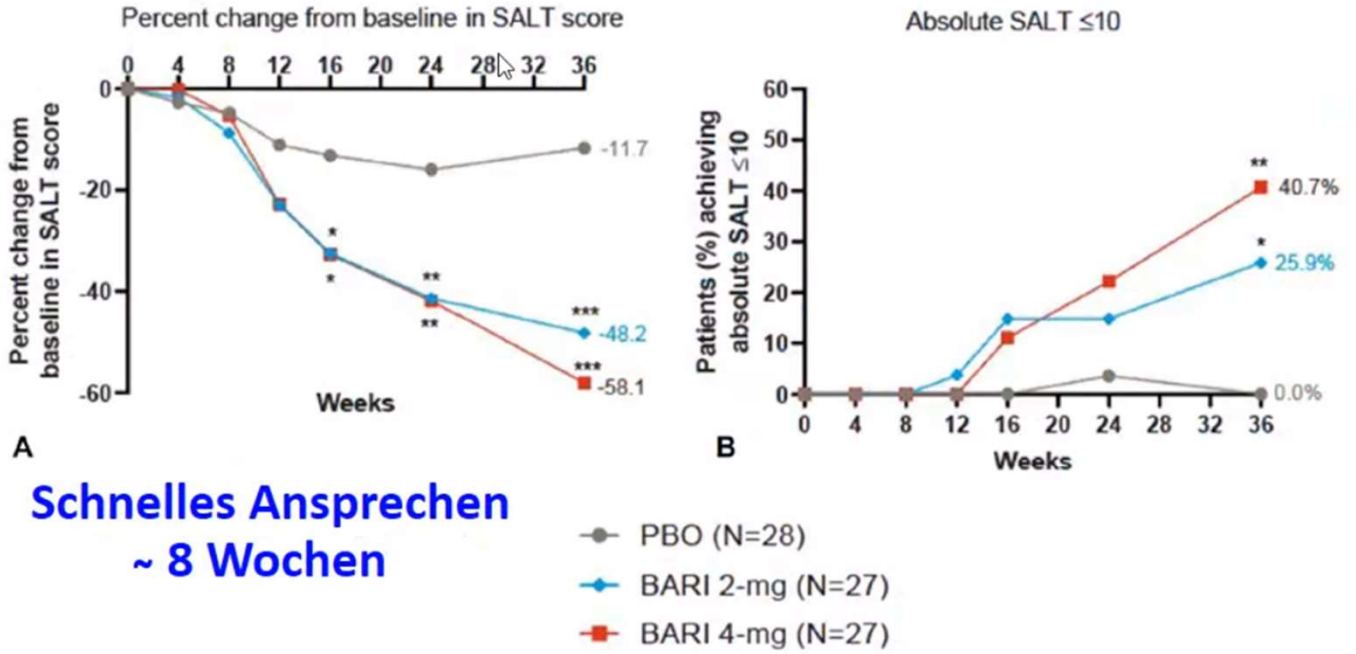


Fig 1. Proportion of patients achieving SALT score ≤20 during 36 weeks of treatment. The figure shows outcomes for the IAS population at week 36. $*P < .05$, $***P \leq .001$ versus PBO. *BARI*, Baricitinib; *IAS*, interim analysis set; *N*, number of patients in each treatment group; *PBO*, placebo; *SALT*, Severity of Alopecia Tool.

Alopecia areata

Baricitinib

Auch fast komplette Remissionen (SALT ≤10)



Schnelles Ansprechen ~ 8 Wochen

Fig 2. A, Percent change in SALT score from baseline through week 36. **B,** proportion of patients achieving an absolute SALT score ≤10 through week 36. *$P < .05$, **$P \leq .01$, ***$P \leq .001$ versus PBO. *BARI*, Baricitinib; *N*, number of patients in each treatment group; *PBO*, placebo; *SALT*, Severity of Alopecia Tool.

Alopecia areata

Ritlecitinib und Breprocitinib

Table II. Summary of adverse events, serious adverse events, and discontinuations in the safety analysis set

Adverse events	Placebo (n = 47)	Ritlecitinib (n = 48)	Brepocitinib (n = 47)
Total number of AEs	105	82	124
Patients with AEs, n (%)	35 (74)	32 (67)	36 (77)
Patients with serious AEs, n (%)	0	0	2 (4)
Deaths, n (%)	0	0	0
Patients discontinuing study drug due to AEs and continuing study, n (%)	1 (2)	2 (4)	2 (4)
Patients discontinuing study due to AEs, n (%)	2 (4)	0	2 (4)
AEs occurring in > 5% of patients in a study group, n (%)			
Upper respiratory tract infection	5 (11)	4 (8)	11 (23)
Nasopharyngitis	6 (13)	6 (13)	4 (9)
Headache	5 (11)	6 (13)	4 (9)
Acne	2 (4)	5 (10)	5 (11)
Nausea	5 (11)	3 (6)	3 (6)
Diarrhea	3 (6)	4 (8)	1 (2)
Abdominal discomfort	4 (9)	0	1 (2)
Sinusitis	2 (4)	0	3 (6)
Viral upper respiratory tract infection	0	2 (4)	3 (6)
Folliculitis	1 (2)	3 (6)	1 (2)
Atopic dermatitis	0	3 (6)	1 (2)
Neutrophil count decreased	1 (2)	0	3 (6)
Abdominal pain	0	0	3 (6)
Fatigue	3 (6)	0	0
Oropharyngeal pain	0	0	3 (6)

Data have been rounded to the nearest integer. Adverse events are all causality. The safety analysis set includes all patients who received at least 1 dose of study drug.

AE, adverse event; *n*, number of patients.

Rhabdomyolyse

HNO-Infekte

Alopecia areata

Topische JAK-Hemmer?

Clinical Trial > J Am Acad Dermatol. 2020 Feb;82(2):412-419. doi: 10.1016/j.jaad.2019.10.016. Epub 2019 Oct 14.

Ruxolitinib cream for the treatment of patients with alopecia areata: A 2-part, double-blind, randomized, vehicle-controlled phase 2 study

Elise A Olsen [1], Deanna Kornacki [2], Kang Sun [3], Maria K Hordinsky [4]

Affiliations + expand

PMID: 31622643 DOI: 10.1016/j.jaad.2019.10.016

Abstract

Background: There are currently no treatments for alopecia areata (AA) that are universally effective or approved by the US Food and Drug Administration. Oral ruxolitinib has shown efficacy in extensive AA. Ruxolitinib cream would potentially avoid systemic adverse effects.

Objective: To assess the efficacy and safety of 1.5% ruxolitinib cream in patients with AA who had at least 25% hair loss by Severity of Alopecia Tool score.

Methods: This was a 2-part study. Part A was an open-label, 24-week study of 1.5% ruxolitinib cream in patients with 25% to 99% hair loss followed by a 24-week extension period. Part B was a double-blind, vehicle-controlled, 24-week study of 1.5% ruxolitinib cream in patients with 25% to 100% hair loss, followed by a crossover to ruxolitinib cream in the vehicle group for 24 weeks and additional treatment time for the ruxolitinib cream group.

Results: Although Part A results suggested potential efficacy of 1.5% ruxolitinib cream, there was no significant difference in hair regrowth based on 50% improvement in Severity of Alopecia Tool scores between patients receiving 1.5% ruxolitinib cream and vehicle in part B. There were no significant safety issues with 1.5% ruxolitinib cream.

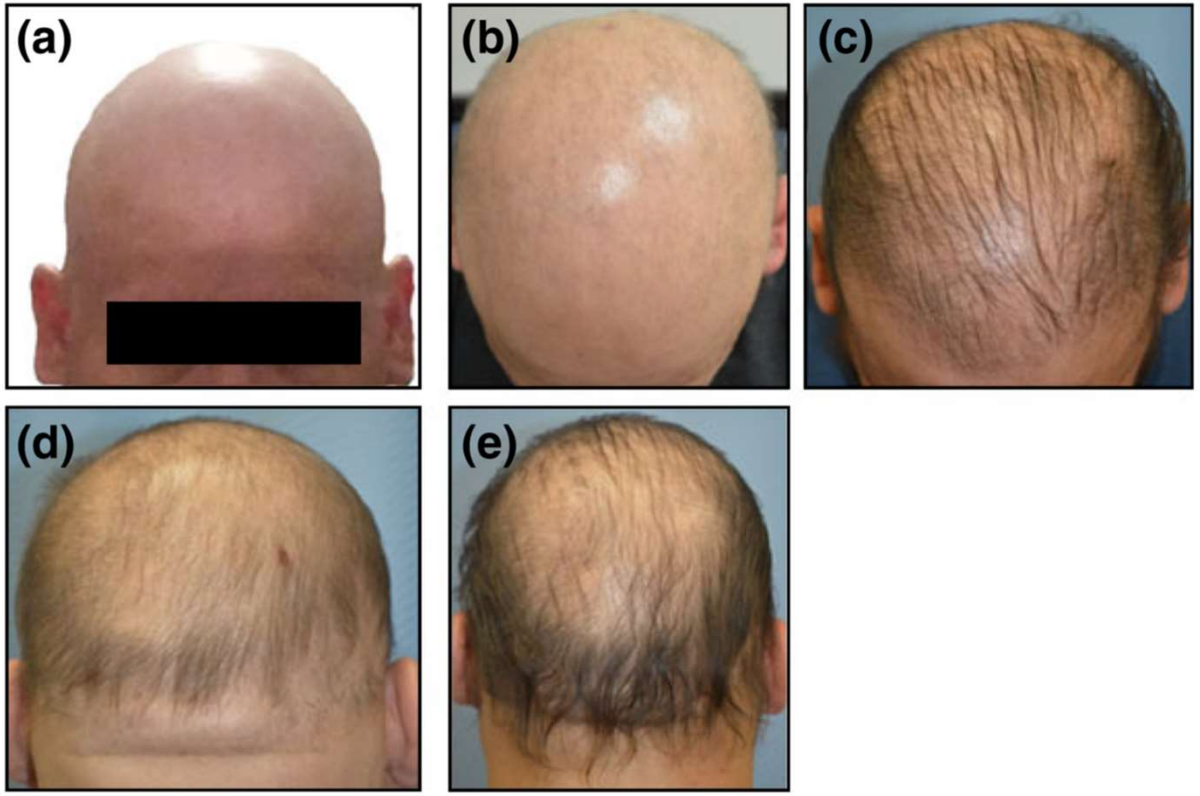
Limitations: Single strength of ruxolitinib cream.

Conclusions: The 1.5% ruxolitinib cream did not have a significant effect in patients with AA.

Keywords: alopecia areata; clinical trial; ruxolitinib cream

- 2-armige Studie an Patienten mit SALT ≥25
- Ruxolitinib 1,5 %-Creme
- Part A open-label 24 Wochen mit Extension für 24 Wochen
- Part B doppelblind, Vehikel-kontrolliert für 24 Wochen, dann crossover zu Verum für 24 Wochen

Erste Erfahrungen mit JAK-Inhibitoren bei der Alopecia areata



Gupta et al. J Eur Acad Dermatol Venereol. 2016 Aug;30(8):1373-8

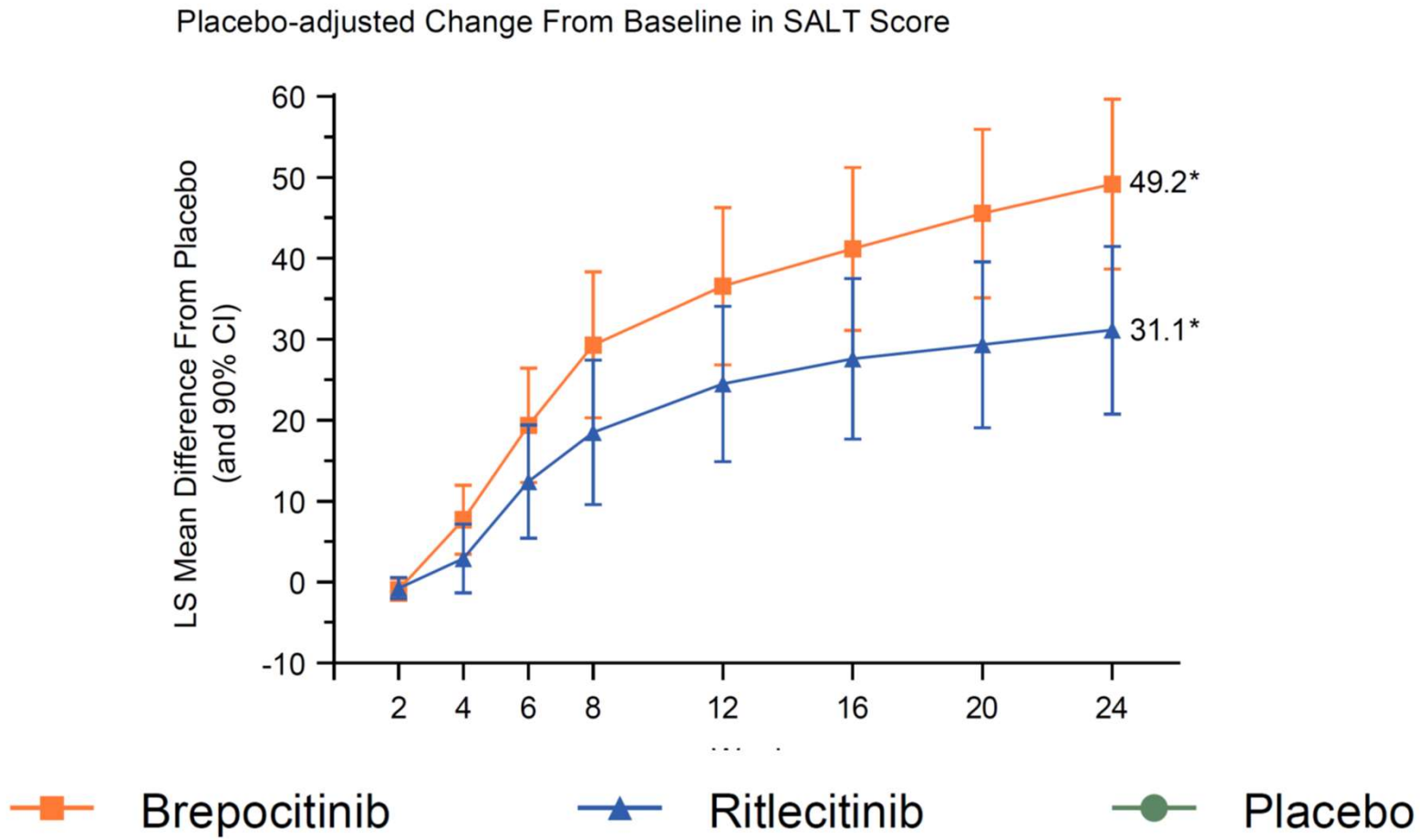
Erste Erfahrungen in Studien

–

A phase 2a randomized, placebo-controlled study to evaluate the efficacy and safety of the oral Janus kinase inhibitors ritlecitinib and brepocitinib in alopecia areata: 24-week results

King et al. J Am Acad Dermatol. 2021 Aug;85(2):379-387

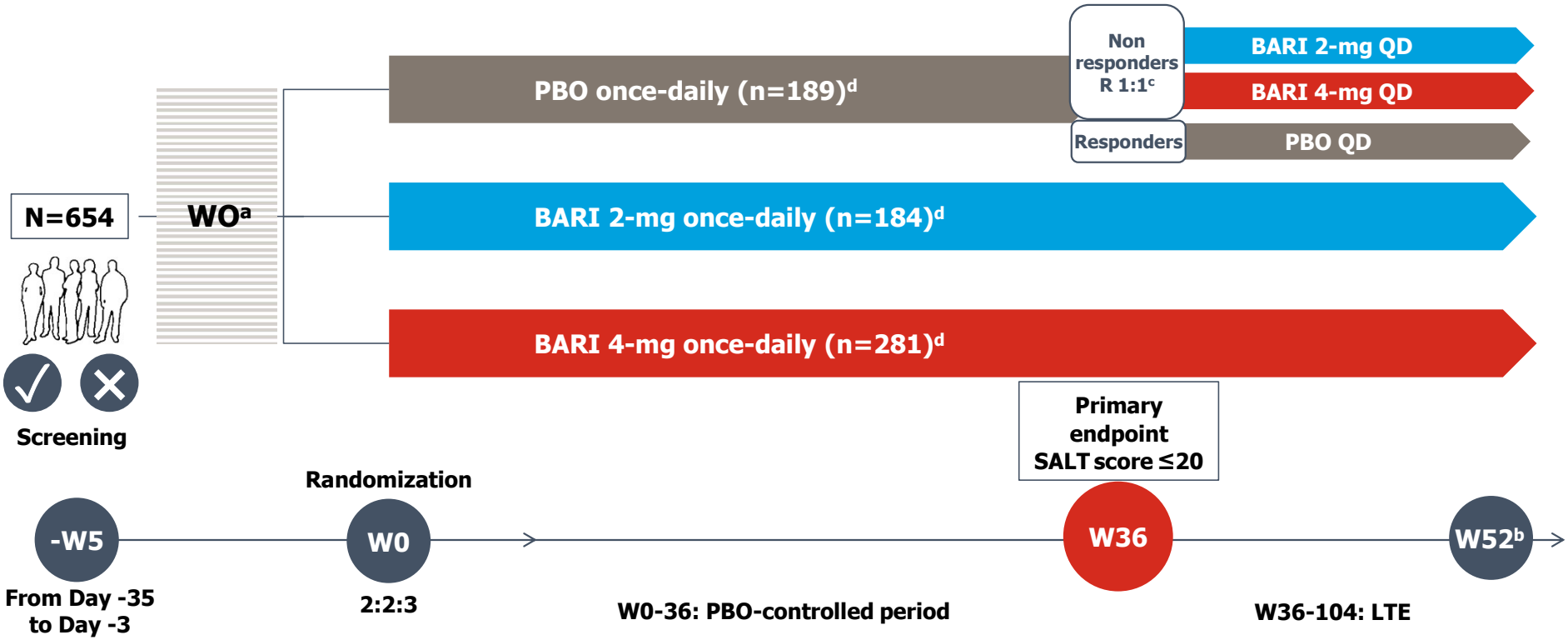
Wiederwachstum der Haare unter Therapie



Weitere Studien

King et al. N Engl J Med. 2022 May 5;386(18):1687-1699

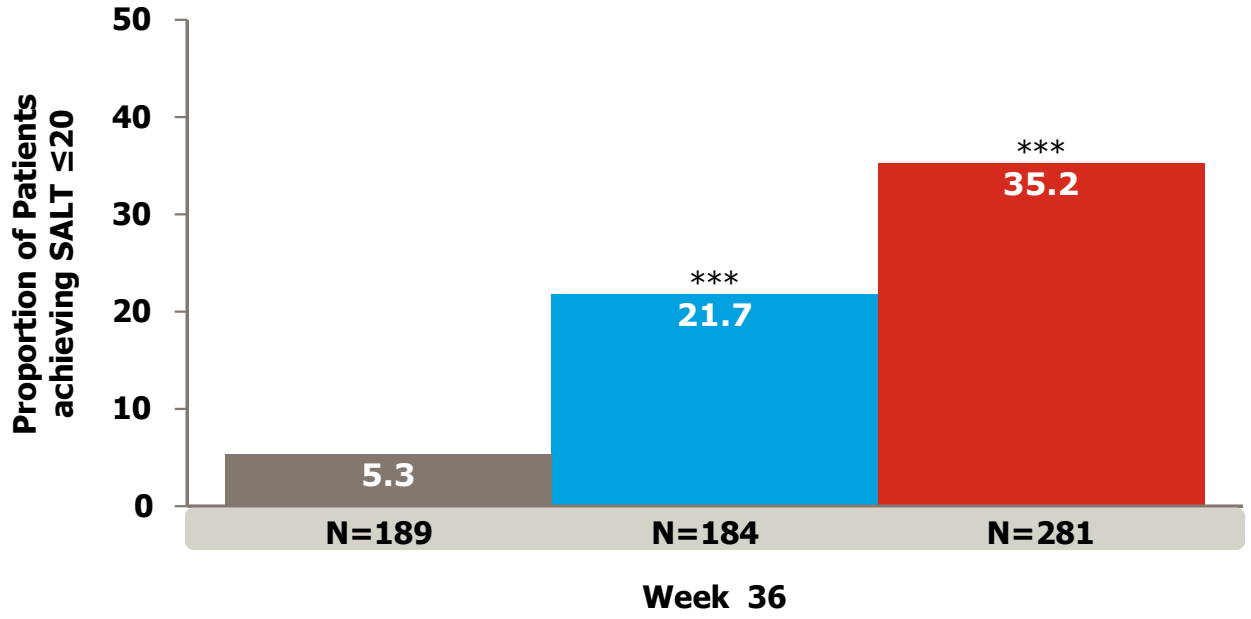
STUDY DESIGN, BRAVE-AA1



[a]Duration of WO (-35 days to -3 days) dependent the treatment. [b]At Week 52, eligible patients from the BARI 2-mg and 4mg arms will enter randomized withdrawal. Subjects who have completed Week 104 and have not met criteria of permanent discontinuation will have the possibility to remain in the trial for up to 96 additional weeks (to Week 200; Bridging Extension); [c]Non responders = SALT >20.
[d]Discontinued treatment prior to Week 36: PBO n=21 (11.1%); BARI 2-mg n=16 (8.7%); BARI 4-mg n=19 (6.8%).

BARI=baricitinib; LTE=long-term extension; PBO=placebo; SALT=Severity of Alopecia Tool; QD=once-daily; W=week; WO=washout

Patientenanteil mit mindestens 80% Kopfbehaarung nach 36 Wochen Therapie



p-value vs. PBO
***p≤0.001; **p≤0.01; *p≤0.05

NRI=non-responder imputation
AA=alopecia areata; BARI=baricitinib; PBO=placebo; SALT=Severity of Alopecia Tool

JAK-Inhibitoren in der Entwicklung für die Alopecia areata

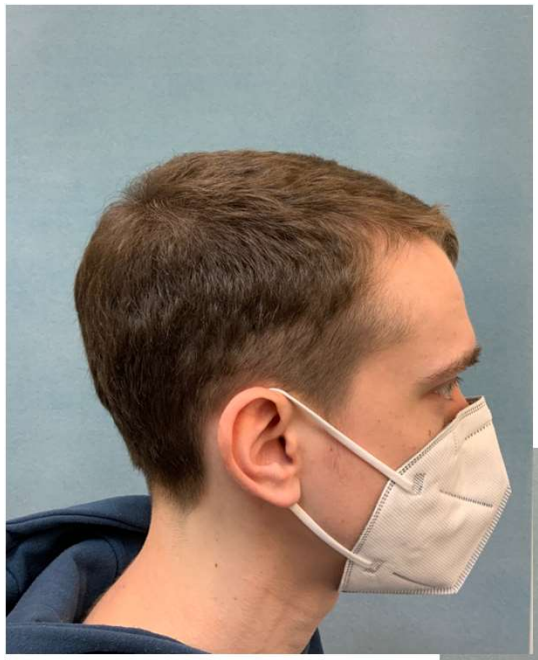
- Brepocitinib
- Ritlecitinib
- Baricitinib
- CTP-543

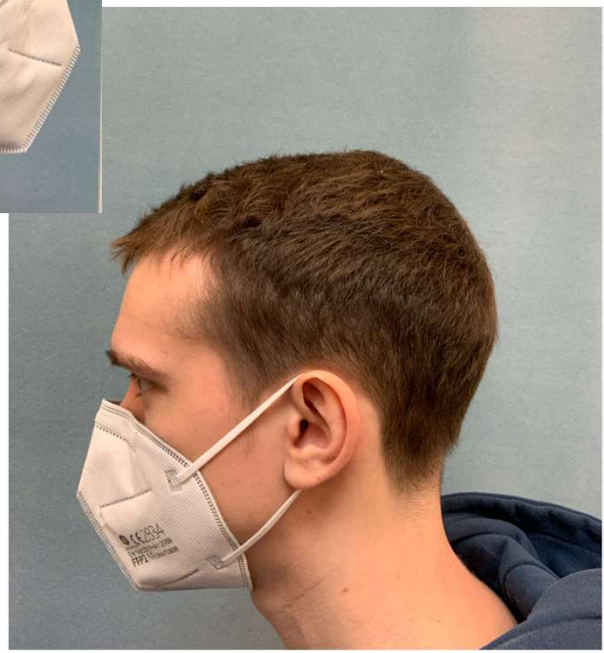
Eigene Erfahrungen mit JAK-Inhibitoren bei der Alopecia areata

Teilnahme an zahlreichen klinischen Studien:

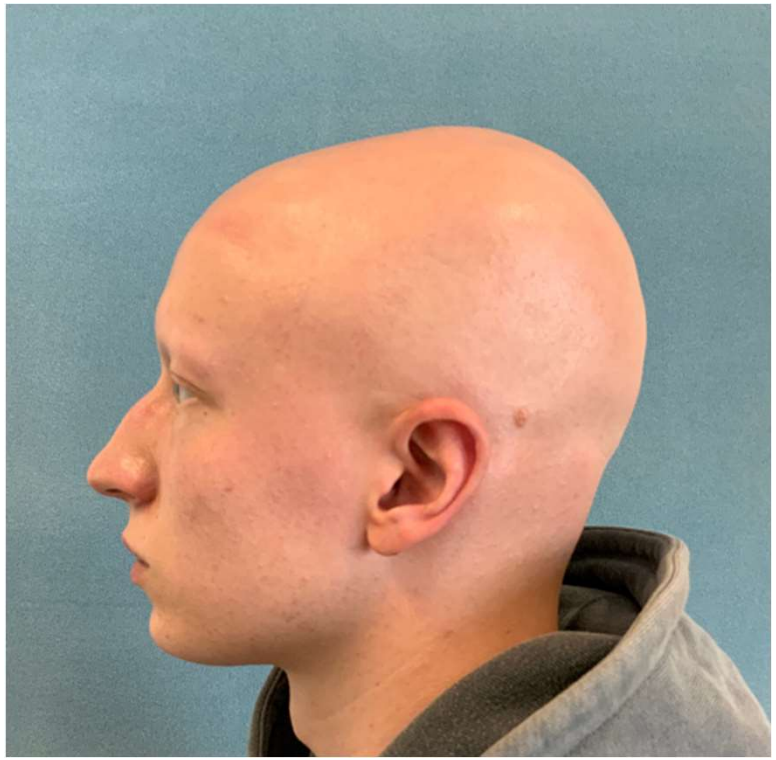
- Studien Protokoll Nr. B7981015 (Ritlecitinib)
- Studien Protokoll Nr. B7981032 (Ritlecitinib)
- Studien Protokoll Nr. CP543.3002 (CTP-543)
- Studien Protokoll Nr. CP543.5002 (CTP-543)

vor Therapie

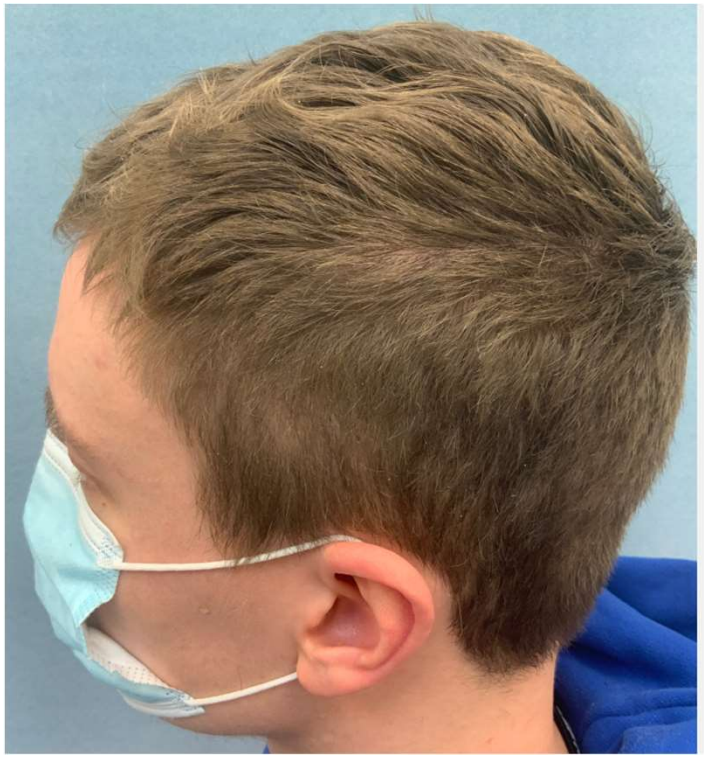




nach 5 Monaten



vor Therapie



nach 5 Monaten

Report

Treatment of alopecia universalis with topical Janus kinase inhibitors – a double blind, placebo, and active controlled pilot study

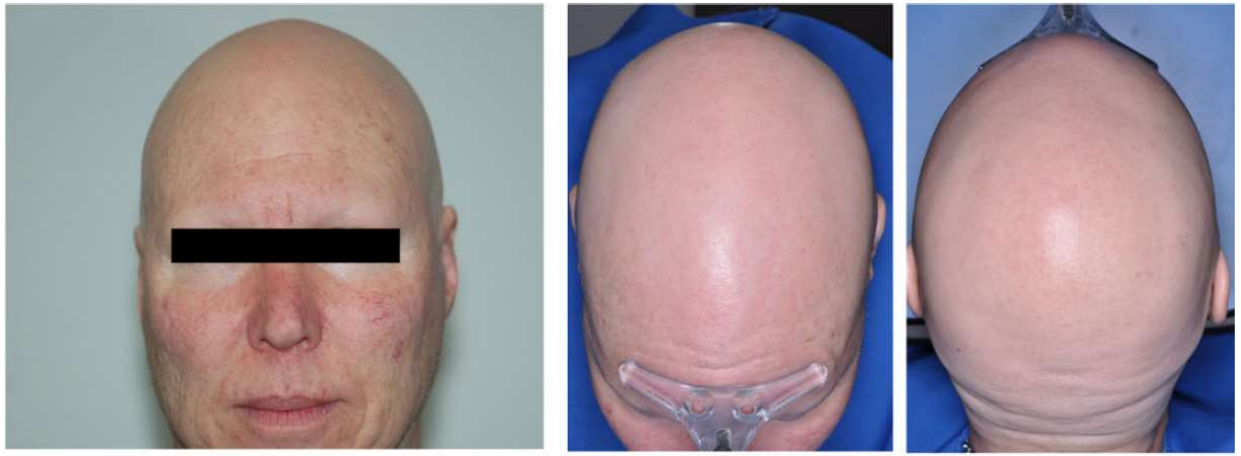
Laita Bokhari, MPhil Med, and Rodney Sinclair, MBBS, MD, FACD

- topische Ruxolitinib Lösung
- topische Tofacitinib Lösung

Bokhari et al. Int J Dermatol. 2018 Dec;57(12):1464-1470

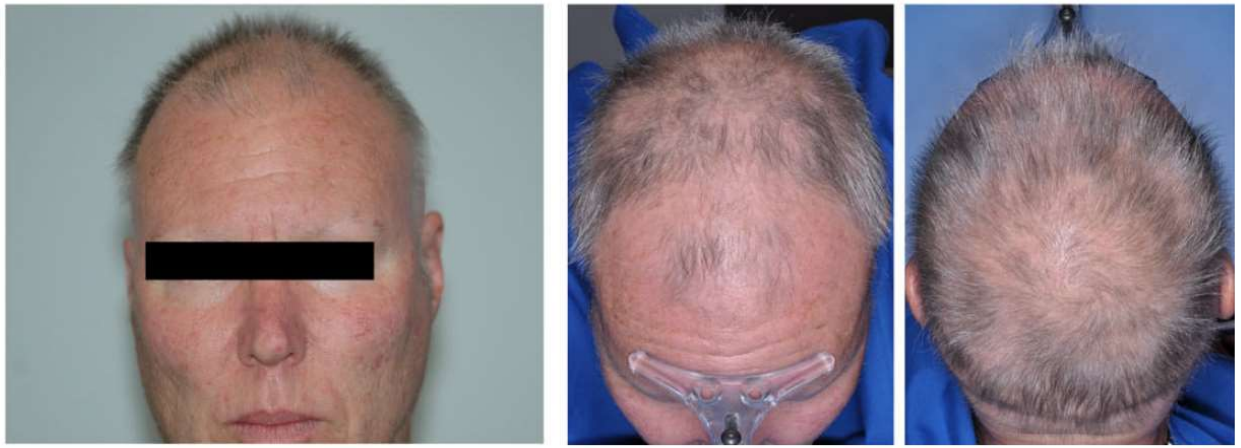
vor Therapie

Baseline



After 12 weeks of topical treatment

nach 12 Wochen



Bokhari et al. Int J Dermatol. 2018 Dec;57(12):1464-1470

Augenbrauen

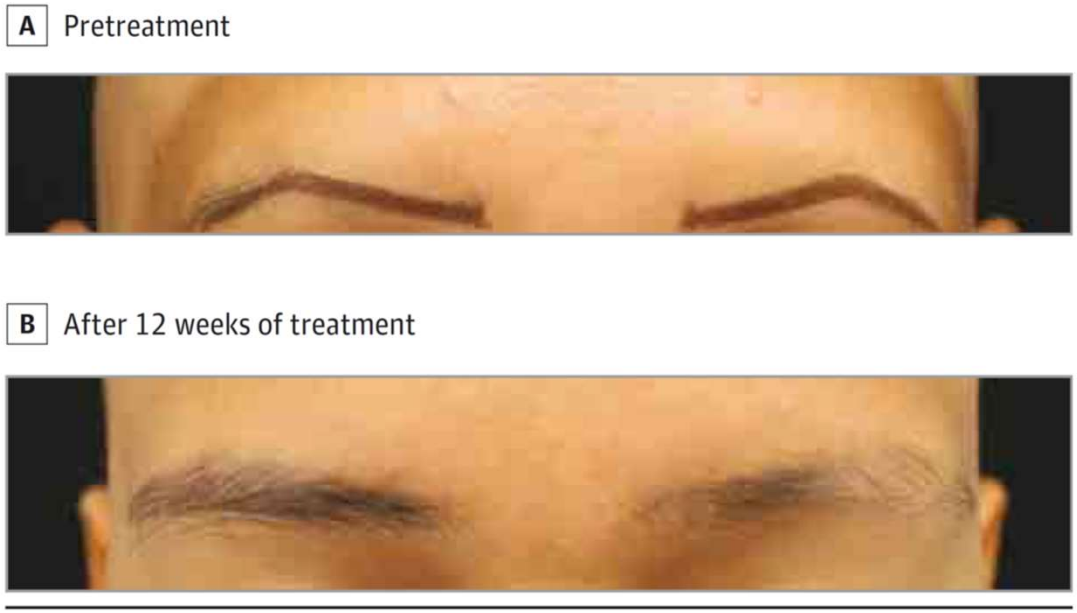
vor Therapie

angemalte Augenbrauen

Craiglow et al. JAMA Dermatol. 2016 Apr;152(4):490-1

Augenbrauen

vor Therapie



angemalte Augenbrauen

nach 12 Wochen

Craiglow et al. JAMA Dermatol. 2016 Apr;152(4):490-1

Sicherheitsprofil von JAK-Inhibitoren

- durch immunabsenkende Wirkung erhöhte Infektrate
- Gürtelrose
- Lippenherpes
- Acne
- sehr selten Thrombosen / Lungenembolie
- Bei rheumatologischen Patienten:
  in Einzelfällen Lungenkrebs aufgetreten

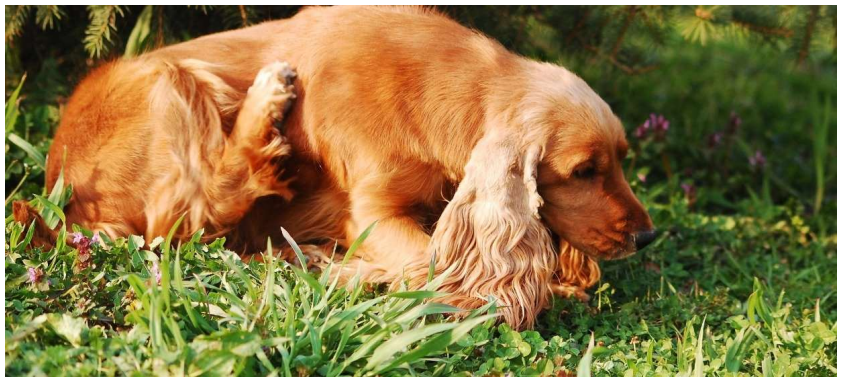
→ mehr Nebenwirkungen v.a. ältere Patienten (65 und älter)
→ Risikofaktor für Nebenwirkungen: Fettleibigkeit, Immobilität

Wie geht es mit den JAK-Inhibitoren weiter?

- Zulassung wird geprüft (USA), in Europa kurz vor Zulassung
- Werden Kosten von den Krankenkassen übernommen…?
- Bislang werden Haarwuchspräparate nicht von der Krankenkasse erstattet (gelten als Lifestyle-Produkte)
- Jahrestherapiekosten ≈15.000 €

JAK-Inhibitoren in der Tiermedizin

20 Tabletten
28,35 €



Weitere neue Therapieansätze

CONCISE COMMUNICATION

BJD
British Journal of Dermatology

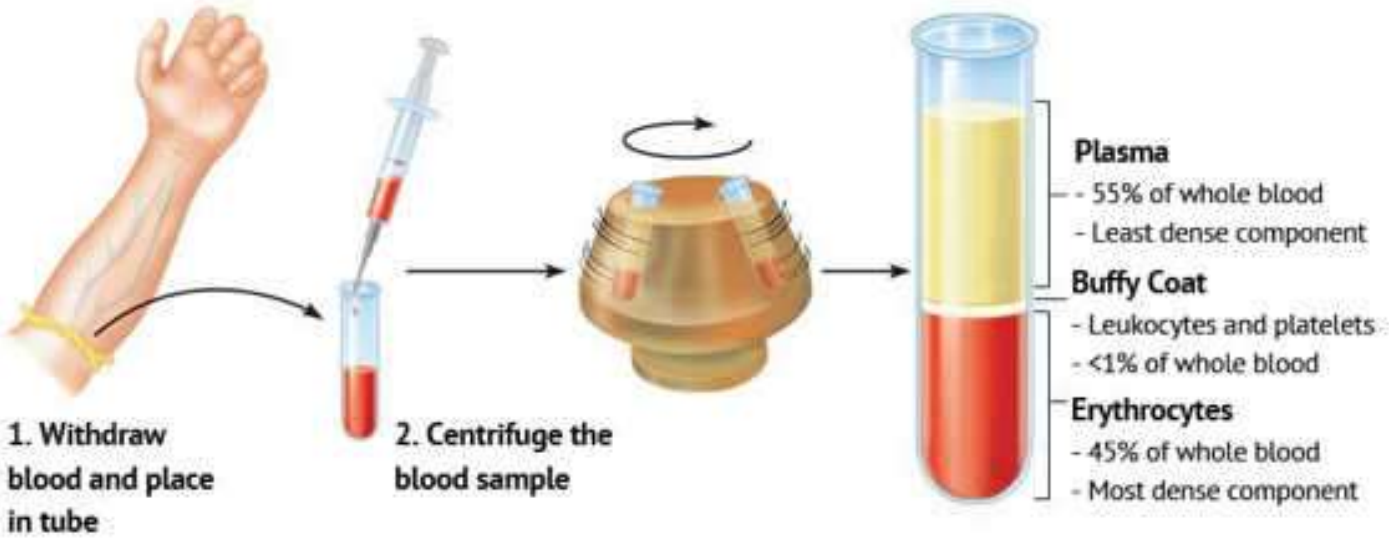
A randomized, double-blind, placebo- and active-controlled, half-head study to evaluate the effects of platelet-rich plasma on alopecia areata

Platelet-rich Plasma (PRP)

Blutplasma (Eigenblut-Therapie)

Trink et al. Br J Dermatol. 2013 Sep;169(3):690-4

Hintergrund Blutplasma-Therapie (PRP)

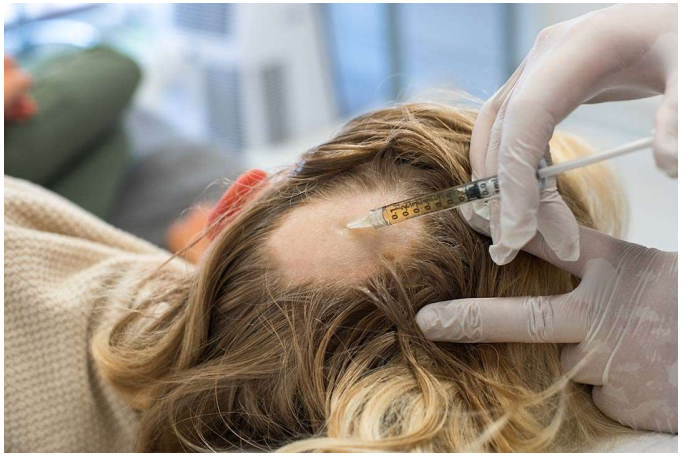


Hintergrund Blutplasma-Therapie (PRP)

Blutplasma enthält:

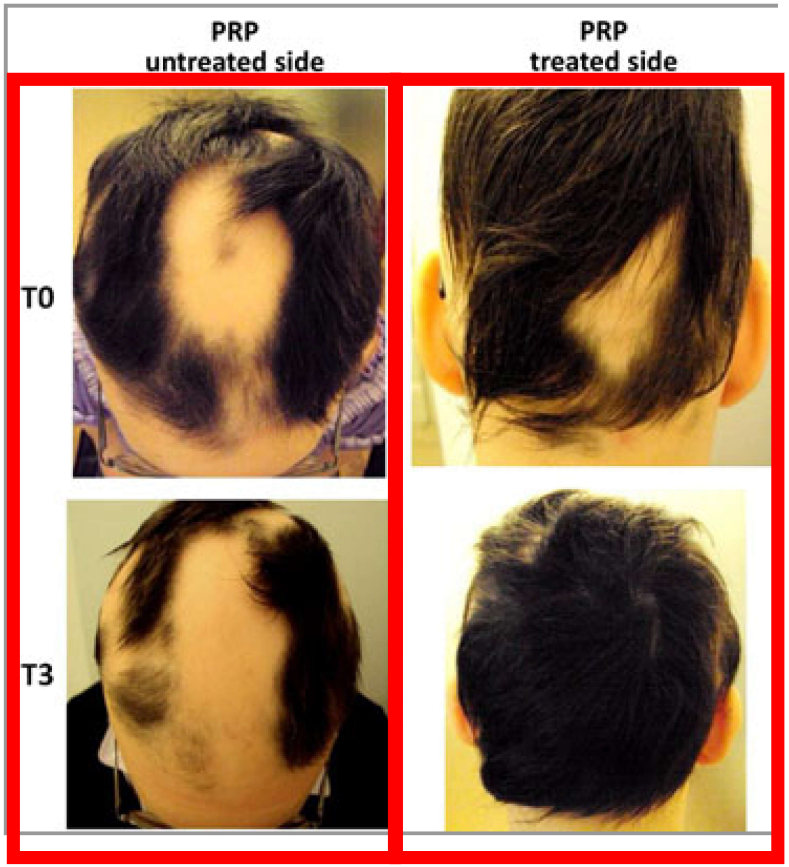
- antientzündliche natürliche Wirkstoffe
- Wachstumsfaktoren für Haarwurzeln

Therapieplan PRP: Alopecia areata



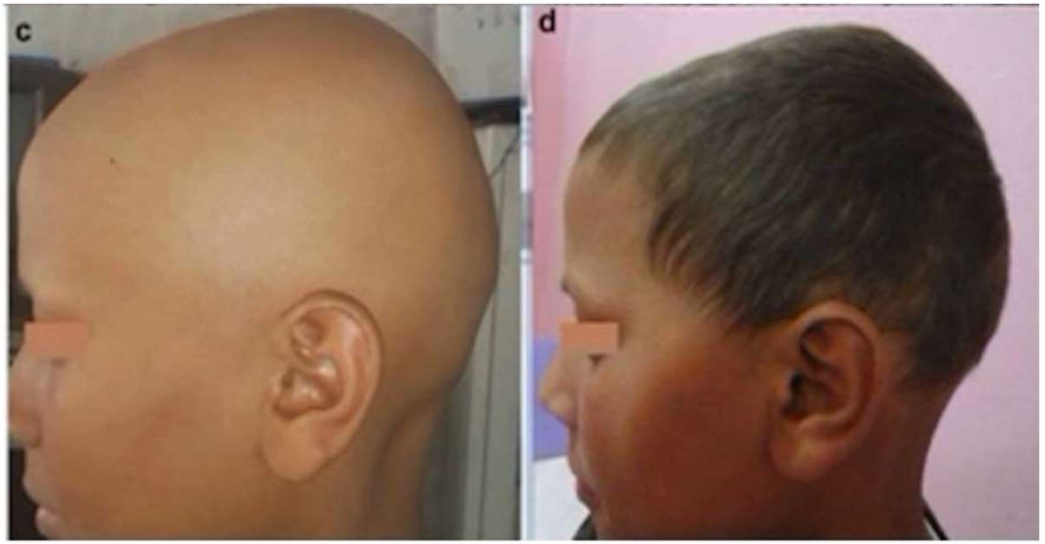
- monatliche Injektionen in haarlose Areale
- Effekte nach 3 Monaten
- nach Erreichen des Therapieeffekts Verlängerung des Therapieintervalls
- Wirkung nur in behandelten Arealen

Therapieplan PRP: Alopecia areata



unbehandelt behandelt

- Monatliche Injektionen in haarlose Areale
- Effekte nach 3 Monaten
- Nach Erreichen des Therapieeffekts Verlängerung des Therapieintervalls
- Wirkung nur in behandelten Arealen

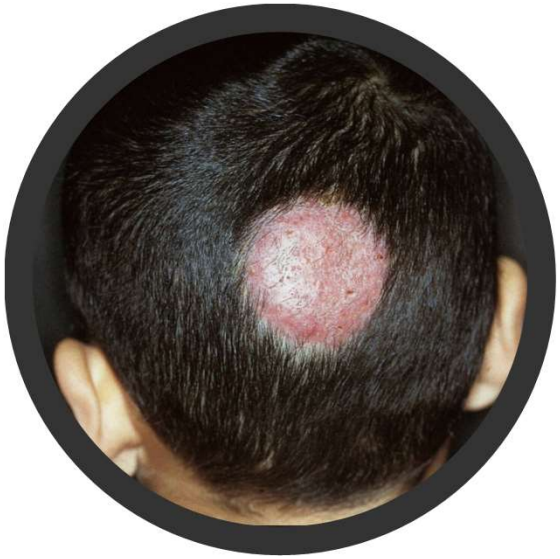


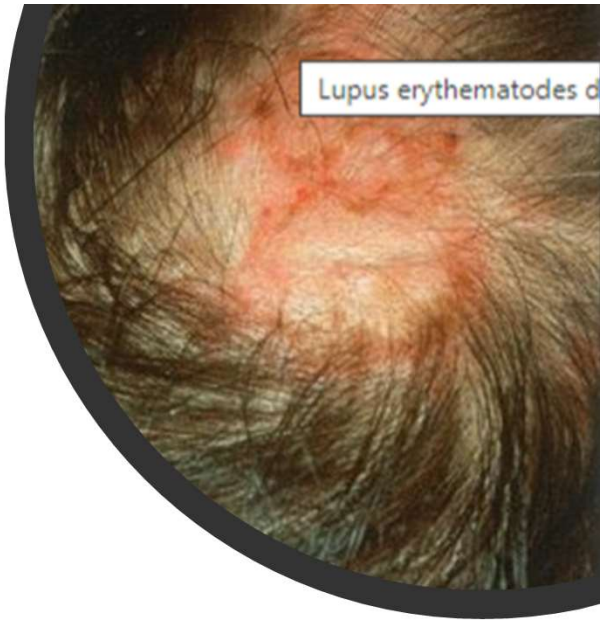
Sicherheitsprofil der PRP-Therapie

- keine schweren Medikamenten-Nebenwirkungen
- körpereigene Stoffe
- Injektion (Blutung, Schmerz, Schwellung)
- Kopfschmerzen
- Kosten (keine Kassenzulassung)

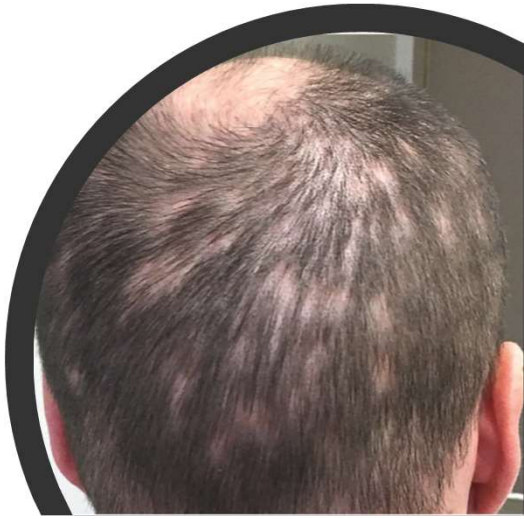
gruppiert nach Kindern/Jugendlichen und Erwachsenen.

	DD Umschriebene Alopecia areata	DD diffuse Alopecia areata
Kinder/Jugendliche	Tinea capitis	loses Anagenhaar Syndrom
	Trichotillomanie	telogenes Effluvium
	temporale trianguläre Alopezie (N. Breuer)	kongenitale Hypotrichose
liche/Erwachsene	follikuläre Muzinosen	telogenes Effluvium
	Alopecia syphilitica	AGA mit weibliche Haarausfallmu
	vernarbende Alopezie, CDLE, Lichen	medikam





Differenzialdiagnosen



PRP-Therapie bei Alopecia areata

→ ab September 2022 auch in Bad Bentheim

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Vielen Dank für Ihre Aufmerksamkeit!

Armina Schulte

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Fachklinik
Bad Bentheim

Rheumatologie · Dermatologie
Orthopädie · Kardiologie