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Direktor: Prof. Dr. med. Kamran Ghoreschi

HABILITATIONSSCHRIFT
„GEZIELTE THERAPIEN DER PSORIASIS“

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von

Dr. Georgios Kokolakis

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Dekan: Prof. Dr. Axel Radlach Pries
1. Gutachter: Prof. Dr. Kilian Eyerich
2. Gutachter: Prof. Dr. Falk Bechara

Inhaltsverzeichnis

1. Abkürzungsverzeichnis

BSA Body Surface Area

ca. zirka

CD Cluster of Differentiation

CED chronisch-entzündliche Darmerkrankung

DLQI Dermatology Life Quality Index

DC dendritische Zellen

IL Interleukin

IFN Interferon

JAK Janus Kinase

NAPSI Nail Psoriasis Severity Index

NK-Zellen Natural-Killerzellen

NMSC non-melanoma skin cancer

PsA Psoriasis Arthritis

Pso Psoriasis vulgaris

PASI Psoriasis Area and Severity Index

PNHK Primary Normal Human Keratinocytes

SCC Squamous Cell Carcinoma

STAT Signal Transducer and Activator of Transcription

Th T-Helferzellen

TNF Tumor Necrosis Factor

TGF Tumor Growth Factor

z.B. zum Beispiel

z.T. zum Teil

2. Einleitung

2.1. Psoriasis

Psoriasis ist eine chronisch-entzündliche Erkrankung, die außer der Haut und den Nägeln auch die Enthesen und die Gelenke betreffen kann (1). Die Prävalenz der Psoriasis wird in der europäischen Population auf ca. 3% geschätzt, wobei beide Geschlechter gleichermaßen häufig betroffen sind (2).

Die häufigste klinische Variante der Psoriasis ist die so genannte Psoriasis vulgaris oder Plaque-Typ Psoriasis. Klinisch manifestiert sich die Psoriasis vulgaris mit scharf begrenzten, erythematosquamösen Plaques mit silbriger, groblamellärer Schuppung v.a. an den Streckseiten der Extremitäten. Auch die Kopfhaut, der Rumpf sowie die intertriginösen Hautareale, wie z.B. die Achselhöhle, Leiste oder die Rima ani, können von Psoriasis betroffen sein. Aufgrund des hohen Feuchtigkeitsniveaus erscheint die Psoriasis in den intertriginösen Arealen, als Psoriasis inversa bezeichnet, wie ein mazeriertes, scharf begrenztes Erythem (2). Basierend auf dem klinischen Bild der Psoriasis und der Ausprägung der Hautbeteiligung kann der Schweregrad der Plaque-Typ Psoriasis mit der Hilfe des Psoriasis Area and Severity Index (PASI) von 0 bis 72 quantifiziert werden (3).

Die Eigenheiten der Anatomie des Nagelapparates und die besondere Verhornung der Nagelplatte führen zu einer charakteristischen Manifestation der Psoriasis der Nägel. Die Veränderungen stammen entweder aus der Nagelmatrix (Grübchen, Onychodystrophie, Leukonychie, rote Flecken in der Lunula) oder aus dem Nagelbett (subungualen Hyperkeratosen, Splitterhämorhagien, Ölflecken und Onycholyse). Der Nail Psoriasis Severity Index (NAPSI) ermöglicht eine objektive Beurteilung der Ausprägung der Nagelpsoriasis (4).

Psoriasis hat einen negativen Einfluss auf die Lebensqualität der Betroffenen. Die Auswirkungen sind weitreichender für junge und weibliche Patienten sowie für Patienten:innen mit ausgeprägtem Hautbefund (5). Anders als erwartet, korreliert die Verbesserung des Hautbefundes nicht immer mit der Besserung der Lebensqualität der Patienten:innen. Eine signifikante Korrelation der 75-prozentigen Besserung der Haut mit der Lebensqualität konnte bei Psoriasispatienten:innen unter Therapie mit Biologika gezeigt werden (6). Die Einschränkung der Lebensqualität von Patienten:innen mit dermatologischen Erkrankungen kann mit der Nutzung eines

validierten und gut etablierten Fragenbogens (Dermatology Life Quality Index; DLQI) objektiviert werden (7).

2.2 Komorbidität der Psoriasis

Psoriasis Arthritis ist die häufigste Komorbidität der Psoriasis. Es wird diskutiert, ob PsA eine Begleiterkrankung oder eine extrakutane artikuläre Manifestation der Psoriasis ist. Das stärkste Argument dafür wäre die fast identische Immunpathogenese (8). In verschiedenen Studien konnte eine Prävalenz von 11-30% bei vorbekannter Plaque-Typ Psoriasis nachgewiesen werden (9-12). Wie bei Pso, sind Männer und Frauen gleich häufig von PsA betroffen, wobei PsA erst ca. 10 Jahre nach der Erstmanifestation von Pso auftritt. Nur bei ca. 15% der Patienten:innen tritt die Arthritis vor der Plaque-Typ Psoriasis auf (10, 13).

Die Prävalenz der PsA konnte mit bestimmten Manifestationen der Psoriasis vulgaris assoziiert werden. Im Vergleich mit Patienten:innen mit einer Plaque-Typ Psoriasis zeigen die Patienten:innen mit einer Psoriasis capitis ein 3.89-fach erhöhtes Risiko PsA zu entwickeln. Bei Patienten:innen mit Nageldystrophie oder Psoriasis inversa ist das Risiko 2.93- bzw. 2.35-fach erhöht (14). Diese Beobachtung sowie die Entwicklung einer PsA, zumeist als Folge der kutanen Manifestation, betonen die wichtige Rolle von Dermatologen in der Früherkennung der PsA.

Die Diagnose der PsA kann auch für erfahrene Rheumatologen herausfordernd sein. PsA ist eine seronegative Arthritis mit einem charakteristischen radiographischen Bild in den späteren Stadien. Die Diagnose wird hauptsächlich klinisch gestellt. Bei entzündlichen Schmerzen von mindestens 3 Monaten können die CASPAR Kriterien verwendet werden, die eine Sensitivität von 91% und eine Spezifität von 99% für die PsA aufweisen. Das aktuelle oder anamnestische Vorhandensein einer Plaque-Typ Psoriasis oder einer Daktylitis, die Nagelbeteiligung, die negativen Rheumafaktoren, und das radiologische Vorhandensein von juxt-artikulären Knochenneubildungen werden in den CASPAR-Kriterien erfasst (15). Die Etablierung sonographischer Befunde und die Entwicklung fluoreszenzoptischer Bildgebungsverfahren haben zu einer schnelleren Diagnose der PsA beigetragen (16). Die Früherkennung der PsA und die zeitnahe Einleitung einer Systemtherapie tragen wesentlich zur Erhaltung der

körperlichen Fähigkeiten der Patienten und zur Vorbeugung von Erosionen in den peripheren Gelenken bei (17).

Die genetische Überlappung und die gemeinsamen immunpathogenetischen Mechanismen der Psoriasis mit chronisch-entzündlichen Darmerkrankungen führen zu einer erhöhten Prävalenz von Morbus Crohn und Colitis ulcerosa bei Psoriasispatienten:innen. Sowohl entscheidende Suszeptibilitätsloci, wie CARDCARD15/NOD2 oder TNFSF15, als auch die prominente Beteiligung der Zytokine der Th-1 Differenzierung von T-Helfer-Zellen, u.a. TNFα, könnte das gleichzeitige Auftreten von Psoriasis und CED erklären (18). In einer großen Kohorte mit 12.502 Psoriasispatienten:innen konnte ein 2,49- bzw. 1,64faches erhöhtes Risiko für die Entwicklung von Morbus Crohn und Colitis ulcerosa nachgewiesen werden. Das Risiko war für Psoriasispatienten:innen im Alter von 20-39 Jahren deutlich erhöht (19).

Psoriasis ist pathogenetisch mit bestimmten metabolischen und psychischen Begleiterkrankungen assoziiert, die das sogenannte Spektrum der Psoriasiskomorbidität erfassen. Für die metabolischen Begleiterkrankungen spielen proinflammatorische Zytokine, wie der TNFα, und Adipokine eine wichtige Rolle (20). Sowohl das metabolische Syndrom als Diagnose als auch jede einzelne Komponente des metabolischen Syndroms treten signifikant häufiger bei Psoriasispatienten:innen als bei der gesunden Bevölkerung auf. Auch der BMI der Patienten:innen mit Psoriasis ist deutlich höher. In Deutschland sind 28,1% der Psoriasispatienten:innen adipös (BMI>30). Das metabolische Syndrom und die Adipositas führen zu einem erhöhten Risiko für kardiovaskuläre Erkrankungen. Psoriasispatienten:innen entwickeln häufig kardiovaskuläre Erkrankungen, wobei diese nicht unbedingt auf ein vorliegendes metabolisches Syndrom zurückzuführen sind (21). Insofern wird die Psoriasis als ein unabhängiger Risikofaktor für kardiovaskuläre Ereignisse gewertet (22).

Depression und Angststörungen sind deutlich häufiger v.a. bei Psoriasispatienten:innen mit einer längeren Krankheitsdauer. Studien zeigen ein Risiko von 1.85 für Depression und eine Rate von 1.47 für Angststörungen im Vergleich zur gesunden Kontrollgruppe (23). Darüber hinaus beeinflussen die Stigmatisierung, das Rauchen und der Alkoholabusus das psychosoziale Profil der Psoriasispatienten:innen zusätzlich negativ (21).

2.3 Histologie der Psoriasis

Das histologische Bild der Psoriasis ist sehr charakteristisch und kongruiert mit den vorliegenden Immunphänomenen. In der Dermis unter der psoriatischen Epidermis erscheinen die Kapillaren vermehrt und dilatiert und verlaufen sehr oberflächlich zwischen den verlängerten Reteleisten der Epidermis. Ein inflammatorisches Infiltrat bestehend aus dendritischen Zellen, Makrophagen und T-Lymphozyten befindet sich in der Dermis. T-Lymphozyten und Neutrophile wandern auch in die Epidermis ein und bilden dort die sogenannten Munro Mikroabszesse. Die von den Immunzellen sezernierten proinflammatorischen Zytokine aktivieren die basalen Keratinozyten, sodass sie schneller proliferieren. Die höhere Proliferation von den Keratinozyten führt zu einer Verdickung des Stratum spinosum (Akanthose) und damit zu einer Verlängerung der Reteleisten der Epidermis. Außerdem werden die Differenzierung und die Apoptose der Keratinozyten verlangsamt. Somit nimmt das Stratum granulosum ab und die Kerne der Keratinozyten bleiben bis zum Stratum corneum erhalten (Parakeratose), was zur festen und dicken Schuppung der Psoriasisplaques führt (24, 25).

2.4 Immunpathogenese der Psoriasis

Inkorrekterweise wurde die Psoriasis bis vor ca. 40 Jahren als eine Erkrankung der Keratinozyten klassifiziert. Diese Theorie konnte allerdings die Komorbiditäten und die besonderen Manifestationen der Psoriasis nicht erklären. Erst 1974 konnten pathologische T-Lymphozyten bei Patienten:innen mit Psoriasis nachgewiesen werden (26). Somit konnte die entscheidende Beteiligung des Immunsystems zur Pathogenese der Psoriasis bestätigt werden.

Sowohl die angeborene als auch die erworbene Immunität sind in die Immunpathogenese der Psoriasis involviert. Die Interaktion zwischen dendritischen Zellen, T-Lymphozyten, neutrophilen Granulozyten, Keratinozyten und Endothelzellen ist entscheidend nicht nur für die Entwicklung, auch für die Chronizität der Psoriasis. Die Überbrückung der angeborenen mit der erworbenen Immunität erfolgt durch Zytokine, wie z.B. TNFα, IFNγ, IL-23 oder IL-17 (2).

Exogene Faktoren, wie z.B. Stress, bakterielle Komponenten, Nikotin oder Medikamente, können im Zusammenhang mit der vorliegenden genetischen

Prädisposition die pathogenetische Kaskade der Psoriasis durch den immunologischen Stress in der Epidermis triggern. Die antigenpräsentierenden Zellen der Epidermis, die unreifen dendritischen Zellen (DC), nehmen die Antigene auf. In der Anwesenheit von u.a. IFNα, TNFα und IL-1β werden die plasmazytoiden dendritischen Zellen aktiviert und als bereits aktivierte myeloide dendritische Zellen migrieren sie in die Lymphknoten. Dort präsentieren die DC die Antigene den naiven T-Zellen (Th0) und induzieren deren Differenzierung entweder zu Th-1 oder Th-17 Zellen (25, 27). Drei Signale sind für die Interkommunikation der DC mit den T-Zellen wichtig. Das erste Signal wird durch die Interaktion von TCR mit MHC II-Komplex vermittelt. Für das zweite Signal sind kostimulierende Zytokine und Liganden, wie CD40, CD80, PD-L1, PD-L2 oder CTLA-4 bedeutend. Wegweisend für die Differenzierung in die Richtung Th1 oder Th17 ist das Signal, welches durch die löslichen Mediatoren vermittelt wird. In Anwesenheit von IL-12 und mit der verstärkenden Wirkung von IFNγ, werden die naiven T-Zellen in die Richtung Th1 polarisiert. Infolgedessen werden sie Zytokine der Th1 Palette, wie IFNγ, IL-22, IL-26, TNFα oder TNFβ, produzieren. Wenn IL-6, IL-23 und TGFβ während der Aktivierung von naiven T-Zellen durch die DC anwesend sind, werden die Th0 in den Th17 Differenzierungsweg geführt. Die Th17 Zellen produzieren hauptsächlich IL-6, IL-17 und IL-22. Die intrazellulären Signale der Th1 Zellen sind vor allem von STAT4 abhängig, während für die Th17 Zellen STAT1, STAT4 oder STAT6 wichtig sind. In der Pathogenese der Psoriasis und damit als therapeutischer Ansatzpunkt sind TNF-α, IL-17 und IL-23 besonders bedeutend.

Unabhängig vom Differenzierungsweg wird die Aktivierung von naiven T-Zellen zur Entwicklung von Effektor-T-Zellen, Effektor-Gedächtnis-T-Zellen oder zentralen Gedächtnis-T-Zellen führen. Die Effektorzellen wandern dann in die Dermis bzw. Epidermis. Die Effektor-Gedächtnis-Zellen zirkulieren zwischen Blut und peripherem Gewebe und produzieren schnell Zytokine nach Stimulation. Die zentralen Gedächtnis-Zellen zirkulieren zwischen Blut und Lymphknoten (25).

Die Lymphozyten rollen in den Blutgefäßen. Das führt zur Inflammation des Endotheliums. In der psoriatischen Haut exprimieren die Endothelzellen deutlich mehr P- und E-Selektin als Folge der Stimulation hauptsächlich durch den TNFα. Diese Adhäsionsmoleküle verlangsamen das Rollen der Lymphozyten. Mittels Diapedese fliehen die Lymphozyten aus den Gefäßen und migrieren ins Gewebe.

Andere Immunzellen, wie z.B. neutrophile Granulozyten, NK-Zellen oder Monozyten/Makrophagen migrieren durch ähnliche Prozesse in die entzündete Haut (27). Die „Mikroinflammation“ des Endotheliums zusammen mit den neu identifizierten *low-density* Granulozyten und den mitinvolvierten Zytokinen, u.a. TNFα, IL-17, IL-22, wurden als mögliche Ursache der metabolischen und kardiovaskulären Komorbiditäten der Psoriasis diskutiert (28).

Sobald die Th1 und Th17 Zellen die Dermis erreicht haben, produzieren sie die entsprechenden proinflammatorischen Zytokine. Sowohl die Th1 Zytokine, v.a. TNFα und IFNγ, als auch die Th17 Zytokine, wie IL-17, aktivieren die Keratinozyten. Die Keratinozyten reagieren auf diese Stimuli und produzieren selbst proinflammatorische Zytokine und Chemokine, wie TNFα, IL-1β, IL-6, IL-17, CXCL8-CXCL11 und CCL20, sowie antimikrobielle Peptide (S100) (25, 27). Wiederum aktivieren die von den Keratinozyten produzierten proinflammatorischen Zytokine die Immunzellen, sodass dies zu einem Teufelskreis zwischen Epidermis und dermalem inflammatorischen Infiltrat führt (25).

Außerdem erhöht sich durch die Stimulation der proinflammatorischen Zytokine die Proliferationsrate der Keratinozyten ca. fünfzigfach und deren Apoptose und Differenzierung werden gehindert (24, 29). Diese Phänomene führen zu Akanthose, Verlust des Stratus granulosum und Parakeratose, den charakteristischen pathologischen Zeichen der psoriatischen Epidermis (27).

Ein erhöhter Spiegel von TNFα wurde in den Psoriasisplaques und im Serum von Psoriasispatienten nachgewiesen (30). Der lösliche TNFα ist ein nicht-glykosyliertes Protein, welches als ein Trimer von 51kDalton zirkuliert. Die vorläufige Form bleibt an der Zellmembran gebunden und wirkt durch den direkten Kontakt mit Nachbarzellen (31). Die Bindung an den spezifischen transmembranen Rezeptoren, TNF-Rezeptor-1 und -2, triggert die JAK-abhängigen intrazellulären Signale. Als Folge davon wird der NFκB aktiviert und in den Zellkern verlegt. Dadurch wird die Expression von proinflammatorischen Zytokinen und Adhäsionsmolekülen induziert (32).

Die IL-17 Familie besteht aus IL-17A und den strukturell ähnlichen IL-17B, IL-17C, IL-17D, IL-17E und IL-17F, die entweder als IL-17A und IL-17F Homodimere oder IL-17A/IL-17F Heterodimere durch die Bindung an die IL17RA, IL17RC und IL17RE Rezeptoren die inflammatorischen Signale übermitteln. Synergistisch mit anderen Zytokinen, wie z.B. TNFα, IL-22 oder IFN-γ werden die IL-17 Signale verstärkt (33).

Das IL-23 ist ein Heterodimer bestehend aus p19 und p40 Subeinheiten. Die p40 ist eine gemeinsame Subeinheit von IL-23 und IL-12, welches aus p40 und p35 Subeinheiten formuliert wird. Das IL-23 ist der Hauptpromotor für die Differenzierung der naiven T-Zellen zu Effektor- und Gedächtnis-Th17-Zellen und stabilisiert die Zytokin-produzierenden pathogenen Th17-Zellen (27, 33).

Die Immunpathogenese der Psoriasis Arthritis und der Enthesitis als Frühmanifestation der Arthritis ähneln der der Plaque-Typ Psoriasis. Auch wenn die Zielzellen sich eindeutig unterscheiden, die Immunzellen und die involvierten Zytokine sind identisch.

Myeoloide DC und v.a. plasmazytoide DC sowie angeborene lymphoide Zellen sind in der Synovialflüssigkeit von Psoriasis Arthritis Patienten:innen nachgewiesen worden. Das von den dendritischen Zellen sezernierte IL-12 und IL-23 wird dementsprechend die Differenzierung der naiven T-Zellen in Richtung Th1 oder Th17 fördern. Auch die Makrophagen des Synoviums und die fibroblastenähnlichen Synoviozyten spielen eine wichtige Rolle bei der Induktion der Entzündung in der Psoriasis Arthritis. Das entzündete Synovium führt zu einer Schädigung des Knorpels und der Knochen. Durch die Produktion von Matrix-Metalloproteinasen von fibroblastenähnlichen Synoviozyten kommt es zur Fibrillierung der Knorpelöberfläche und Chondrozyten werden apoptotisch. Interessanterweise werden in PsA Knochenerosionen und Osteophyten an den gleichen Lokalisationen beobachtet. Die osteolytischen Prozesse sind begrenzt und finden sehr nah am Periost statt. Darüber hinaus sind die osteoblastischen Reparaturmechanismen aktiviert, um die Homöostase der Knochen zu gewährleisten. Sowohl die Erosionen als auch die reaktive Osteogenese sind für die Funktionalität des Gelenks einschränkend (34, 35).

2.5. Therapie der Psoriasis

Dank des besseren Verständnisses der Pathogenese sind in den letzten Jahren hochwirksame gezielte Therapien für die Psoriasis entwickelt worden. Eine wirksame Therapie verbessert nicht nur den Hautbefund der Betroffenen, sondern auch deren Lebensqualität und unterbricht die inflammatorische Kaskade und ihre Konsequenzen.

Die Therapie erfolgt nach dem Schweregrad der Erkrankung und der Begleiterkrankungen, v.a. dem gleichzeitigen Vorhandensein einer PsA.

Der Schweregrad der Pso wird nach dem PASI-, BSA- und DLQI-Score eingeschätzt. Nach der aktuellen Leitlinie wird die Psoriasis als mild (PASI<10 und DLQI<10) oder mittelschwer-schwer (PASI>10 und DLQI>10) eingestuft. In einem Graubereich, in der die Haut wenig betroffen (PASI<10) und die Lebensqualität sehr eingeschränkt ist (DLQI>10), kann die Therapie von topisch auf systemisch eskaliert werden. Voraussetzung dafür ist der Befall von besonderen Lokalisationen (palmoplantar, intertriginös, Nägel, sichtbare Areale) und das Auftreten von subjektiven Beschwerden (Schmerz, Juckreiz, Schlafstörung) (36).

Für die milde Psoriasis wird zunächst eine topische Therapie mit Calcipotriol/Betamethason empfohlen. Außerdem kommen topische Kortikosteroide oder Vitamin-D-Analoga als Monotherapie und Teerderivate, Keratolytika oder auch topische Calcineurin-Inhibitoren zum Einsatz (37).

Eine Systemtherapie ist bei der mittelschwer-schweren Form der Psoriasis indiziert. Die Systemtherapien sind in drei Gruppen eingeteilt: die breit-wirkenden klassischen Immunsuppressiva, die Biologika und die gezielten niedermolekularen Verbindungen (small-molecules).

Die Fumarsäureester sind seit 1995 für die Therapie der Psoriasis zugelassen. Der Wirkmechanismus von Fumarsäureestern ist wenig gut beschrieben. Neben ihrem Effekt an den CD4+ und CD8+ T-Zellen können die Fumarsäureester die Aktivierung und die Anzahl von Neutrophilen reduzieren (38). Bei der Initiierung der Therapie muss die Dosis von Fumarsäreestern titriert werden und die Erhaltungsdosis liegt bei 30 bis 720mg täglich. Eine 75%ige Besserung des PASI Scores konnte bei 40,3% der Patienten unter Dimethylfumarat nach 16 Wochen beobachtet werden. Lymphopenie, gastrointestinale Beschwerden und Flushing, als Substanz-spezifische Nebenwirkungen, können die Anwendung von Fumasäureestern einschränken (39).

Methotrexat ist ein Folsäureantagonist, der in den 60er Jahren als Chemotherapeutikum des Mamma-Karzinoms entwickelt worden ist. Seitdem ist MTX in einer niedrigen immunmodulierenden Dosis (7,5-22,5mg) einmal wöchentlich oral oder subkutan für die Therapie der Plaque-Typ Psoriasis und der PsA zugelassen. Eine Besserung des Hautbefundes zu 75% (PASI75) erreichen 41% der

Patienten:innen. Lebertoxizität, Leukopenie, gastrointestinale Beschwerden und Teratogenität sind die wichtigsten Nebenwirkungen von Methotrexat (40).

Ciclosporin A ist ein Calcineurin-Inhibitor, der die Aktivierung von T-Zellen blockiert. Aufgrund der breiten Immunsuppression kann das Ciclosporin A bei verschiedenen immunologischen Krankheiten angewendet werden. Seit 1993 ist Ciclosporin A in einer Dosierung 2.5-5 mg/kg KG für die Therapie der Pso zugelassen (41). PASI75 wird bei ca. 71% der Patienten:innen nach 16 Wochen erreicht (42). Unter der Therapie mit Ciclosporin A können eine reversible Nephrotoxizität mit nephrogener Hypertonie, Lebertoxizität oder Plattenepithelkarzinome als Nebenwirkungen auftreten (41).

Weniger wirksam als die o.g. Therapien für Psoriasis ist das Acitretin, ein Vitamin-A-Säure Derivat, welches die Aktivierung von Retinoidrezeptoren hemmt. Aufgrund der fehlenden immunsupprimierenden Eigenschaften ist das Acitretin in manchen Situationen besonders wertvoll. Acitretin ist seit 1993 für die Therapie der Plaque-Typ Psoriasis zugelassen. Jedoch ist seine Anwendung aufgrund der Nebenwirkungen, u.a. Lebertoxizität, Lipidstoffwechselstörung, Teratogenität, nur bei bestimmten Patientengruppen möglich (41).

Die ersten gezielten Psoriasistherapien waren die Inhibitoren von TNFα. Zu dieser Gruppe gehören das Fusionsprotein Etanercept, die humanen bzw. humanisierten Antikörper Adalimumab, Golimumab, Certolizumab-pegol sowie der chimäre Antikörper Infliximab. Etanercept, Adalimumab, Certolizumab-pegol und Infliximab sind sowohl für die Plaque-Typ Psoriasis als auch für die Psoriasis Arthritis und die axiale Spondylarthritis zugelassen. Golimumab ist ausschließlich für die Psoriasis Arthritis und die axiale Spondylarthritis zugelassen. Bakterielle und virale sowie opportunistische Infektionen, Tuberkulose, Reaktivierung von Hepatitis B, demyelinisierende Erkrankungen und maligne Erkrankungen u.a. nicht-melanozytäre Hauttumore sind die häufigsten Nebenwirkungen der Klasse von TNFα-Inhibitoren. Trotz allem haben die TNFα-Inhibitoren, als erste Klasse der Biologika, die Therapie der Psoriasis revolutioniert. Die Wirksamkeit konnte nicht nur an den Hautmanifestationen, sondern auch den Arthritisbeschwerden und der radiologischen Progression der PsA in verschiedenen Studien nachgewiesen werden (10).

Um die Differenzierung von Th1-Zellen und als Folge davon die Produktion von Typ-1 Zytokinen und u.a. TNFα zu blockieren, wurden monoklonale Antikörper gegen die

p40-Einheit des IL-12 entwickelt. Da p40 eine gemeinsame Einheit von IL-12 und IL-23 ist, wird nebst IL-12 auch das IL-23 neutralisiert. Von den zwei anti-p40-Antikörpern Briankinumab und Ustekinumab in der Entwicklungsphase wurde nur das Ustekinumab für die Plaque-Typ Psoriasis und die PsA zugelassen (43-45). Durch die gleichzeitige Blockade von IL-12 und IL-23 hat diese Klasse von Therapien eine noch höhere Wirksamkeit für die Psoriasis mit einem günstigeren Sicherheitsprofil gezeigt. Das IL-23 führt zu der Inhibition der Differenzierung von naiven T-Zellen in die Th-17 Richtung und hemmt damit die Produktion von Th-17-Zytokinen, wie z.B. IL-17 oder IL-22 (33).

Die weitere Entwicklung von gezielten Psoriasistherapien fokussierte sich auf die Th-17 Differenzierung. Secukinumab war der erste Antikörper in dieser Klasse, der das IL-17A blockiert. Darüber hinaus repräsentieren Ixekizumab als anti-IL-17A Antikörper, Brodalumab als IL17RA-Rezeptor Antagonist und neuerlich Bimekizumab als IL-17A und IL-17F Antikörper die weitere Entwicklung der Therapien der anti-IL-17 Klasse. Die IL-17-Inhibitoren sind sowohl bei der Plaque-Typ Psoriasis als auch der Psoriasis Arthritis und axialen Spondylarthritis gut wirksam. Aufgrund der Blockade von IL-17 können die anti-IL17 Therapien nebst den allgemeinen Nebenwirkungen eine chronisch-entzündliche Darmerkrankung triggern oder Candida-Infektion der Barriereepithelien verursachen (46, 47).

Guselkumab, Tildakizumab und Risankizumab sind die ersten selektiven IL-23 Antikörper für die Therapie der Psoriasis. Aufgrund der Selektivität der Inhibition von IL-23 und daher der Blockade der Differenzierung von pathogenen Th-17 Zellen zeigten sie eine hervorragende Wirksamkeit an der Psoriasis ohne das Auftreten von IL-17 klassespezifischen Nebenwirkungen, wie CED oder Candidainfektionen. Durch die wichtige Rolle des IL-23 in der Pathogenese der PsA resultiert die Blockade des IL-23 durch die Antikörper in einem sicheren und wirksamen Therapieansatz auch für die PsA (33).

Außer den monoklonalen Antikörpern, die Zytokine selektiv blockieren, wurden in den letzten Jahren neue Substanzen mit einem niedrigen Molekulargewicht, die sogenannten „small-molecules“, als orale gezielte Therapien der Psoriasis oder auch anderer inflammatorischer Erkrankungen entwickelt. Diese Moleküle penetrieren die Zellen und blockieren intrazelluläre Signale (48). Apremilast ist ein Phosphodiesterase-4 Inhibitor und ist das erste small-molecule, welches für die

Therapie der Psoriasis und PsA zugelassen wurde (49, 50). Darüber hinaus wurden die JAK-Kinase-Inhibitoren Tofacitinib und Upadacitinib für die Therapie der PsA zugelassen (51, 52). Beide JAK-Kinase-Inhibitoren zeigen eine gute Wirksamkeit auch für die Plaque-Typ Psoriasis (51, 53). In einer späten Entwicklungsphase der gezielten oralen Therapien für Psoriasis und PsA im Feld der JAK-Kinase Inhibitoren befindet sich das Deucravacitinib, ein Tyrosin-Kinase-2 Inhibitor (54, 55).

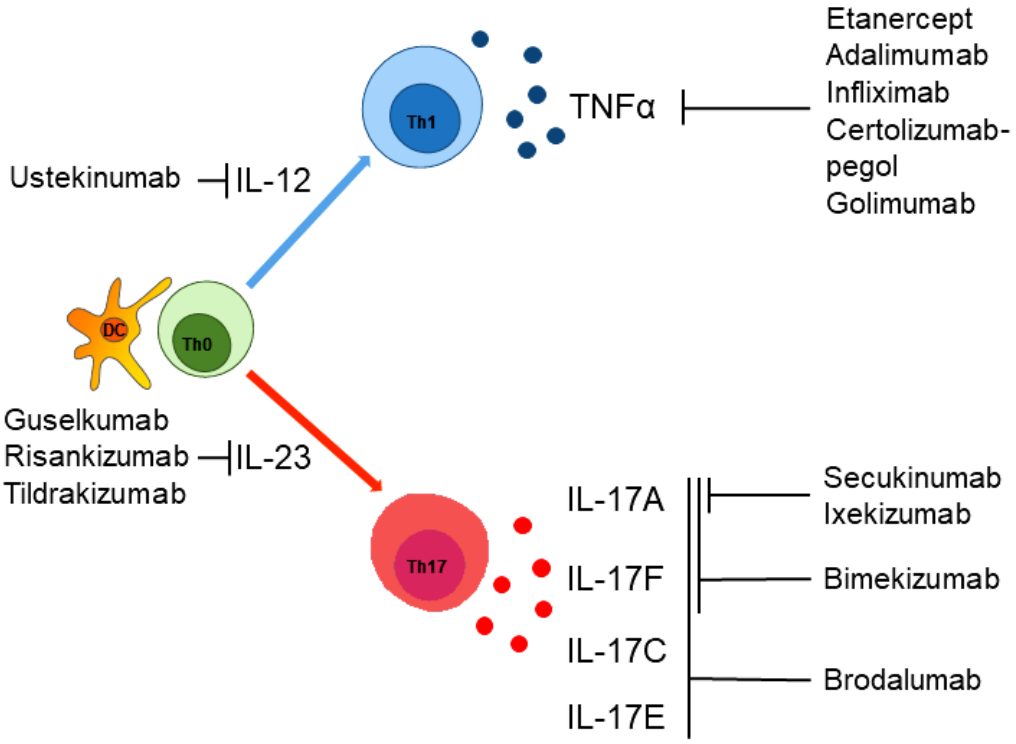

Abbildung 1: Ansatzpunkte der gezielten Psoriasistherapie mit monoklonalen Antikörpern. Abbildung vom Autor erstellt.

3. Eigene Arbeiten

Ambivalent Effects of Tumor Necrosis Factor Alpha on Apoptosis of Malignant and Normal Human Keratinocytes

Skin Pharmacol Physiol. 2021;34(2):94-102. doi: 10.1159/000513725

Kokolakis G, Sabat R, Krüger-Krasagakis S, Eberle J

Das proinflammatorische Zytokin Tumornekrosefaktor-alpha (TNFα) ist sowohl in die Vorgänge der Apoptose als auch die Vorgänge des Zellüberlebens involviert. Durch Bindung von TNF-Rezeptor 1 oder 2 kommt es zur Wirkung des Zytokins. Der TNF-Rezeptor 1 ist vorrangig an der Signalübertragung bei der Apoptose beteiligt. Die apoptotischen Mechanismen in der Zelle können intrinissch über Mitochondrien oder extrinsisch über Todesrezeptoren erfolgen. Todesrezeptorliganden, wie der TNF-Related-Apoptosis-Inducing-Ligand (TRAIL) induzieren spezifisch extrinsische Apoptose, während Zytostatika wie 5-Fluoruracil (5FU) intrinsische Apoptose induzieren. Ziel dieser Arbeit war die Untersuchung der Wirkung von TNFα auf die Apoptose bei malignen und normalen Keratinozyten. Es erfolgte die Stimulierung von Zellen der humanen kutanen Zelllinie Squamous Cell Carcinoma 13 (SCC-13), immortalisierten humanen Keratinozyten (HaCaT) sowie von primären normalen humanen Keratinozyten (PNHK) mit TNFα. Daran wurde entweder die extrinsische oder intrinsische Apoptose mittels TRAIL bzw. 5FU induziert. Eine dosisabhängige Induktion von Apoptose wurde mit verschiedenen Konzentrationen von TRAIL untersucht. Um unspezifische Effekte auszuschließen, wurde die Wirkung von TNFα mit dem monoklonalen anti-TNFα Antikörper Infliximab neutralisiert. Die Zellviabilität, Zellproliferation, Apoptose, Zytotoxizität sowie Expression von Caspase-3 wurden mit entsprechenden Verfahren untersucht (WST-Zellproliferationstest, DNA-Fragmentation ELISA, Durchflusszytometrie, kolorimetrische Analyse der Lactatdehydrogenase, Western Blot). In der vorliegenden Studie konnte ein synergistischer Effekt von TNFα in Kombination mit 5FU und TRAIL auf die Zellviabilität der Zelllinien SCC-13 und HaCaT nachgewiesen werden. Hier zeigte sich eine Verstärkung der apoptotischen Effekte von sowohl den intrinsischen als auch extrinsischen Stimuli. Ein Effekt von TNFα auf die Zellviabilität der Zelllinie PNHK konnte nicht gezeigt werden. Die Vorstimulation mit TNFα hatte einen schützenden Effekt auf die TRAIL- und 5FU-abhänigige Apoptose. Diese Effekte zeigten sich für TNFα spezifisch und dosisabhängig. Die apoptotischen Effekte führten zu der Spaltung von Pro-caspase-3. Es konnten entgegengesetzte Effekte von TNFα in malignen im Vergleich zu normalen humanen Keratinozyten gezeigt werden. Der TNFα fördert die Apoptose von malignen Keratinozyten, wenn sie mit dem Zytostatikum 5FU behandelt werden. Da der TNFα eine wichtige Rolle in der Pathogenese der Psoriasis spielt und dessen Blockade mit monoklonalen Antikörpern oder

Etanercept therapeutisch häufig eingesetzt wird, könnten die Ergebnisse dieser Studie für die Therapieentscheidung von Psoriasispatient:innen relevant sein. Bei Psoriasispatient:innen mit epithelialen Tumoren, wie aktinischen Keratosen oder Plattenepithelkarzinomen, sollte die Blockade von TNFα möglichst vermieden werden.

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The Effect of TNF-Inhibitors on Nail Psoriasis and Psoriatic Arthritis —Real-World Data from Dermatology Practice

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Kokolakis G, Sabat R, Fischer I, Gomis-Kleindienst S, Fritz B, Burmester G-R, Ghoreschi K, Ohrndorf S

Bei der Psoriasisarthritis kommt es oft zum Auftreten von Gelenkbeschwerden Jahre nach der Diagnosestellung einer Plaque-Typ Psoriasis. Basierend darauf sollten Dermatolog:innen frühzeitig auf eine PsA untersuchen und dementsprechend behandeln. In der vorliegenden Studie wurden Patient:innen mit Psoriasis vulgaris mit Nagel- und Gelenkbeteiligung unter Therapie mit TNF-alpha-Inhibitoren untersucht. Es erfolgte die Durchführung einer prospektiven, multizentrischen, nicht-interventionellen, offenen Studie mit dem Ziel der Beurteilung der Wirksamkeit einer Dauertherapie mit Adalimumab, Etanercept und Infliximab über einen Zeitraum von 24 Monaten bei Patient:innen mit moderater bis schwerer Psoriasis vom Plaque-Typ und PsA, die dermatologisch betreut sind. Zur Erfassung der krankheitsspezifischen Charakteristika kamen der Psoriasis Area and Severity Index, Nail Psoriasis Severity Index (NAPSI), die Erfassung der Gelenkbeteiligung, der Dermatology Life Quality Index (DLQI) und der Health Assessment Questionnaire (HAQ) zum Einsatz. Im ersten Jahr erfolgte die Erhebung alle 3 Monate, im 2. Jahr alle 6 Monate.

Es erfolgte der Einschluss von 100 Patient:innen mit Plaque-Typ Psoriasis, Nagelpsoriasis und PsA. Drei Monate nach Therapiebeginn zeigte sich eine signifikante Verringerung des NAPSI im Vergleich zu den Ausgangswerten (Mittelwert±SD, 22.9±17.8 vs. 33.8± 21.4; $p < 0.001$). Eine signifikante Reduktion der schmerzhaften und geschwollen Gelenke innerhalb der ersten drei Monate wurde ebenfalls beobachtet; Mittelwerte Baseline 10.8±11.5 zu 6.4±10.3 ($p < 0.001$) und von 6.4±9.5 zu 3.1±7.2 ($p < 0.001$) jeweils. Unter Therapie zeigte sich eine Verbesserung der Beteiligung der distalen Interphalangealgelenke sowie eine Reduktion von DLQI und HAQ Werten.

Insgesamt zeigt sich eine Verbesserung der Beschwerdekontrolle im Bereich der Haut, Nägel und Gelenke sowie der Lebensqualität und Funktionalität. Dermatolog*innen haben eine wichtige Funktion bei der Diagnosestellung und Langzeitbetreuung von Patient:innen mit Psoriasis mit Gelenkbeteiligung.

Journal of *Personalized Medicine*

MDPI

Article

The Effect of TNF-α Inhibitors on Nail Psoriasis and Psoriatic Arthritis—Real-World Data from Dermatology Practice

Georgios Kokolakis [1,2,*], Robert Sabat [1,3], Imma Fischer [4], Susana Gomis-Kleindienst [5], Björn Fritz [5], Gerd-Rüdiger Burmester [6], Kamran Ghoreschi [2] and Sarah Ohrndorf [6]

[1] Psoriasis Research and Treatment Center, Charité—Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, 10117 Berlin, Germany; robert.sabat@charite.de
[2] Department of Dermatology, Venereology and Allergology, Charité—Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, 10117 Berlin, Germany; kamran.ghoreschi@charite.de
[3] Interdisciplinary Group of Molecular Immunopathology, Dermatology/Medical Immunology, Charité—Universitätsmedizin Berlin, 10117 Berlin, Germany
[4] Biostatistik—Tübingen, 72070 Tuebingen, Germany; Imma.Fischer@biostatistik-tuebingen.de
[5] AbbVie Deutschland GmbH & Co. KG, 65189 Wiesbaden, Germany; susana.gomis-kleindienst@abbvie.com (S.G.-K.); bjoern.fritz@abbvie.com (B.F.)
[6] Department of Rheumatology and Clinical Immunology, Charité—Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, 10117 Berlin, Germany; gerd.burmester@charite.de (G.-R.B.); sarah.ohrndorf@charite.de (S.O.)
* Correspondence: georgios.kokolakis@charite.de; Tel.: +49-30-450618333; Fax: +49-30-450518908

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Abstract: Patients with psoriatic arthritis (PsA) often develop joint symptoms years after their initial diagnosis of psoriasis disease; therefore, dermatologists should test for and detect PsA early. In this study, we focused on patients with psoriasis with both nail and joint disease being treated with tumor necrosis factor-α inhibitors by dermatologists. We performed a noninterventional, prospective, multicenter, and open-label study to evaluate the effectiveness of adalimumab, etanercept, or infliximab over 24 months of continuous therapy in patients with moderate to severe plaque-type psoriasis (Pso) and PsA. Disease assessments with the Psoriasis Area and Severity Index, Nail Psoriasis Severity Index (NAPSI), joint assessment, Dermatology Life Quality Index (DLQI), and Health Assessment Questionnaire (HAQ) instruments were performed every 3 months for the first year and twice annually thereafter. The cohort included 100 patients with Pso, nail psoriasis, and PsA. A significant reduction of NAPSI was observed 3 months after therapy initiation compared with the baseline (mean ± SD, 22.9 ± 17.8 vs. 33.8 ± 21.4; $p < 0.001$). Similarly, the mean ± SD number of both tender and swollen joints decreased significantly within the first 3 months of treatment, from 10.8 ± 11.5 to 6.4 ± 10.3 ($p < 0.001$) and from 6.4 ± 9.5 to 3.1 ± 7.2 ($p < 0.001$), respectively. Additionally, the distal interphalangeal joint involvement improved throughout the observation time, and DLQI and HAQ scores decreased. Improvements in control of skin, nail, and joint symptoms were seen, as well as in patients' quality of life and functionality. Dermatologists have an important role not only in PsA diagnosis but also in PsA long-term care.

Keywords: psoriasis; nail psoriasis; psoriatic arthritis; TNFα-inhibitor; DLQI; HAQ; etanercept; adalimumab; infliximab

1. Introduction

Psoriasis is a chronic inflammatory disease that affects skin and nails, entheses, and peripheral and axial joints [1]. In most patients with psoriasis, skin disease precedes joint involvement. Approximately 67% of patients with psoriatic arthritis (PsA) develop the arthritis nearly 10–20 years after the onset of the cutaneous symptoms of the disease [2]. Nail lesions occur in more than 80% of patients with PsA compared with nearly 40% of patients without PsA [3]. Although there is a wide range of systemic therapies currently available for

plaque-type psoriasis (Pso), treatment of nail psoriasis remains challenging [4,5]. Because nail psoriasis significantly affects patients' quality of life (QoL), it belongs to the criteria for upgrading psoriasis severity, when the affected skin is not considered moderate to severe in disease (PASI < 10) but the patient's QoL is impaired (DLQI > 10) [6].

Although Pso is an easy clinical diagnosis based on the presence of well-demarcated erythematous scaly plaques on the predisposed areas, such as elbows, knees, and scalp, diagnosing PsA can be challenging. PsA is a seronegative arthritis with late pathognomonic signs in conventional radiology. Newly developed imaging techniques may be more sensitive for the early diagnosis of PsA [7]. However, to a certain degree, the diagnosis of PsA depends on the presence of diseased skin or nail manifestations on the patient or in the family history, as proposed by the classification criteria for PsA (CASPAR) [8].

Considering the usual course of PsA following the skin manifestations, dermatologists should routinely monitor their patients with psoriasis for joint involvement and early diagnosis of PsA. Dermatologists should simultaneously introduce the appropriate therapy to rapidly improve and control skin and joint symptoms. Depending on the phenotype of psoriasis, the presence of inflammatory signs of joint involvement, comorbidities, imaging, laboratory tests, and screening questionnaires as consensus on the management of PsA in a dermatology setting could be established. Morning joint stiffness, as well as tender and swollen joints, associated with psoriasis are major conditions for suspecting PsA; therefore, close interdisciplinary collaboration or referral to rheumatologists should be considered [9,10].

In addition to nail psoriasis, especially nail dystrophy and pitting, severe Pso, psoriasis duration of more than 25 years, obesity, uveitis, smoking, and genetic factors, such as having the HLA-B27 allele, can increase the risk of PsA development. As treatment outcomes after the clinical manifestation of PsA are poor, identifying patients at risk of PsA early, and treating accordingly, would reduce this risk [11].

Because the pathogenetic mechanisms of both Pso and PsA are common and mainly through T-helper cells (Th)-1 or Th-17 driven, the therapeutic strategies are largely overlapping, with minor exceptions [1,12–14]. Currently, the development of new therapies for PsA follows that of Pso therapies since the effects of the new substances on the skin are directly visible and easier to objectify [1].

In this noninterventional prospective study, we aimed to describe the cohort of patients with PsA and their therapeutic approach in a dermatology setting, including private practice and state and university hospitals, with a focus on tumor necrosis factor-alpha (TNF-α) inhibitors as the first class of biologics for their treatment of Pso. We specifically focused on patients with nail psoriasis with concomitant PsA, the correlation of nail involvement with PsA, and the therapy response of TNF-α inhibitors. We also addressed the therapy monitoring capabilities from the participating dermatology sites.

2. Materials and Methods

2.1. Study Design and Participants

This was a noninterventional, prospective, multicenter, and open-label cohort study to evaluate the effectiveness of adalimumab, etanercept, or infliximab on nail psoriasis over 24 months of continuous therapy in patients with moderate to severe Pso with or without PsA. The study was conducted at 27 different sites in Germany with dermatologists in 12 private practices with experience on PsA therapies, 5 local hospitals, and 10 university clinics. The recruitment was performed from March 2008 until November 2009.

Adult patients with moderate to severe psoriasis, as defined by the "rule of ten" (Psoriasis Area and Severity Index [PASI] > 10, body surface area [BSA] > 10, Dermatological Life Quality Index [DLQI] > 10), who were candidates for systemic treatment with the TNF-α inhibitors etanercept, adalimumab, and infliximab according to licensure and had psoriasis of the fingernails were included in this observational study. The total population was divided into two subgroups: those with and those without confirmed PsA. In the current analysis, only patients in the cohort with confirmed PsA were evaluated.

Any other skin diseases that could interfere with the evaluation of psoriasis, forms of psoriasis other than Pso, or the presence of latent or active tuberculosis, hepatitis B or C, or HIV infection were the main exclusion criteria. Patients unable to understand the questionnaires and adhere to the study procedures were not included.

All participants provided written informed consent before inclusion. The study was approved by the local ethics committee of Charité—Universitätsmedizin Berlin (EA1/236/08) and was conducted according to the principles of the Declaration of Helsinki.

2.2. Clinical Skin and Joint Assessments

The severity of psoriatic skin alterations was evaluated using PASI score and BSA. Nail involvement was estimated using the total Nail Psoriasis Severity Index (NAPSI) score of all fingernails, resulting in scores ranging from 0 to 80. The number of 78 tender and 76 swollen joints and morning stiffness (in minutes) were assessed at all visits by the treating dermatologist.

2.3. Patient-Reported Outcomes

The impact of psoriasis on a patient's QoL was estimated by the DLQI. Disability was measured by the Health Assessment Questionnaire-Disability Index (HAQ-DI) with a range of 0 to 30, where higher scores indicate greater disability. HAQ is a self-reported questionnaire containing 20 items in eight domains, which was developed as a comprehensive measure outcome for general disability of patients with a variety of rheumatic diseases, such as PsA, with scores from 0 (no disability) to 3 (severe disability) [15]. Scores of 0–1 represent mild to moderate disability, scores of 1–2 indicate moderate to severe disability, and scores of 2–3 indicate severe to very severe disability [16].

All assessments were performed at baseline, every 3 months for the first year, and then twice annually for the second year of observation. Participating study centers were advised to keep the same examiner for each patient throughout the study to avoid deviation between the raters.

2.4. Statistics

Statistical calculations were performed using the Statistical Program for Social Sciences version 25.0 (IBM, Armonk, NY, USA) and Microsoft Excel 2013 (Microsoft Corporation, Redmond, WA, USA). Differences between nonpaired samples were tested using the Mann–Whitney U test. Differences between paired samples were analyzed using the Wilcoxon matched-pairs signed-rank test. Differences between frequencies of men and women in NAPSI improvement groups were tested using a chi-square test. The correlations between NAPSI and distal interphalangeal (DIP) joint involvement were analyzed using a two-tailed Spearman's rank correlation test.

3. Results

3.1. Study Population

In total, 100 patients (63% male; mean ± SD age, 49.6 ± 12.4 years) with Pso and nail psoriasis, as well as PsA, with a mean ± SD disease duration of Pso of 20.1 ± 13.7 years and a mean ± SD BMI of 28.7 ± 5.5 kg/m^2 were included in this cohort study. Demographic and clinical characteristics at baseline are presented in Table 1.

3.2. Overall Improvement of Nail and Skin Psoriasis

Three months after the initiation of therapy with anti–TNF-α therapy, a significant reduction of absolute NAPSI scores, from 33.8 ± 17.8 (mean ± SD) at baseline to 22.9 ± 21.4 ($p < 0.001$), was observed. NAPSI radically decreased until month 9 (12.4 ± 14.6), where it reached a plateau, and then continued decreasing until the end of the observational period (8.2 ± 11.2) (Figure 1a). PASI rapidly decreased from 15.0 ± 12.5 (mean ± SD) at baseline to 6.7 ± 8.8 ($p < 0.001$) after 3 months of treatment. A further less prominent reduction in PASI was observed until month 24 (3.6 ± 5.2) (Figure 1b).

Table 1. Demographic and clinical characteristics of patients at baseline.

Characteristic	Value
Age, years, mean ± SD	49.6 ± 12.4
Sex, %	
Female	37.0
Male	63.0
Disease duration, years, mean ± SD	20.1 ± 13.7
BMI, kg/m^2, mean ± SD	28.7 ± 5.5
BSA at baseline, %, mean ± SD	27.5 ± 25.3
PASI at baseline, mean ± SD	15.0 ± 12.5
NAPSI at baseline, mean ± SD	33.8 ± 21.4
Tender joints at baseline, n, mean ± SD	10.8 ± 11.5
Swollen joints at baseline, n, mean ± SD	6.4 ± 9.5
Morning stiffness, %	
Yes	41.0
No	28.0
Unknown	31.0
DLQI at baseline, mean ± SD	12.5 ± 7.4
HAQ at baseline, mean ± SD	0.63 ± 0.61

BMI: body mass index; BSA: body surface area; DLQI: Dermatological Life Quality Index; HAQ: Health Assessment Questionnaire; NAPSI: Nail Psoriasis Severity Index; PASI: Psoriasis Area and Severity Index; SD: standard deviation.

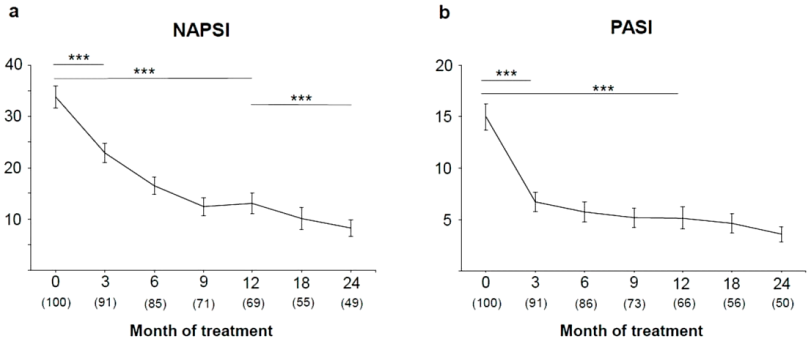

Figure 1. Overall improvement in (**a**) Nail Psoriasis Severity Index (NAPSI) and (**b**) Psoriasis Area and Severity Index (PASI) during therapy. Absolute NAPSI and PASI values (mean ± SEM) and total number of patients per visit are shown. *** $p < 0.001$.

3.3. Impact on PsA

The activity of PsA was estimated by the number of tender and swollen joints out of 78-joint status and 76-joint status, respectively. The number of both tender and swollen joints significantly decreased from a mean ± SD of 10.8 ± 11.5 (78-TJC) and 6.4 ± 9.5 (76-SJC) to 6.4 ± 10.3 and 3.1 ± 7.2, respectively, (both $p < 0.001$) during the first 3 months of treatment. A further reduction of tender and swollen joints could be observed until month 12. The number of swollen joints remained low until month 24 (mean ± SD, 1.8 ± 4.7), whereas the mean ± SD number of tender joints presented a nonsignificant tendency to increase after 18 months (3.9 ± 7.7) until month 24 (5.6 ± 11.8) (Figure 2).

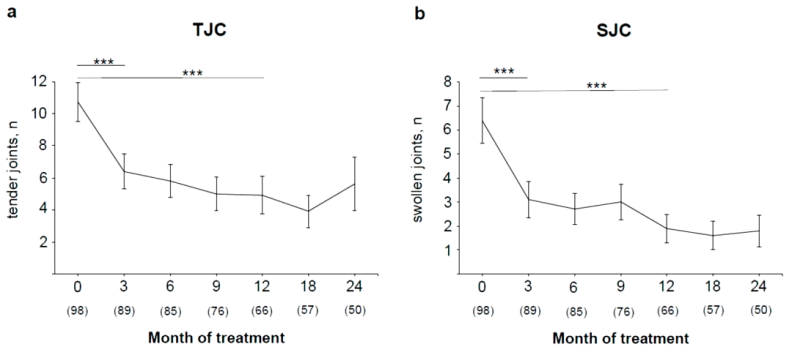

Figure 2. Overall improvement of (**a**) tender joints and (**b**) swollen joints during therapy. Absolute number of tender and swollen joints (mean ± SEM) and total number of patients per visit are shown. *** $p < 0.001$.

To further describe the course of PsA under the therapy with TNF-α inhibitors, the DIP joint involvement was considered as a typical clinical manifestation of PsA in association with nail psoriasis. For that, the DIP of hand/feet were especially considered for tenderness or swelling. A significant reduction of the number of swollen joints in the transverse PsA manifestation was determined from 35% at baseline to 8% after 24 months ($p < 0.001$), prominently being observed in the first 3 months (Figure 3).

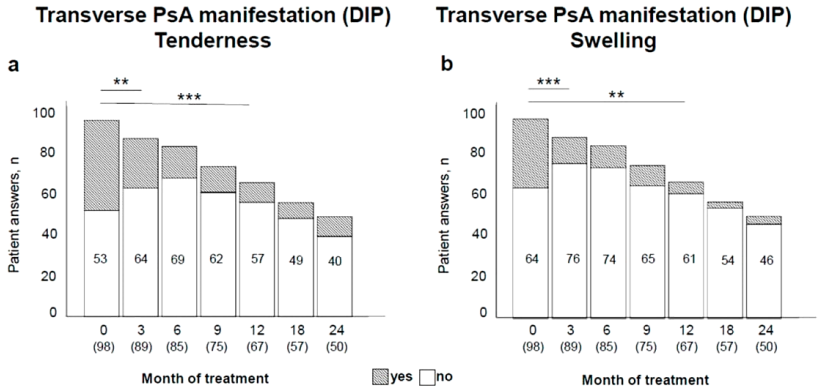

Figure 3. Course of transversal and longitudinal involvement of psoriatic arthritis (PsA) during therapy. In the analysis of transverse joint affection, only the distal interphalangeal (DIP) joints of hand/feet were examined (**a**,**b**). Yes/No refers to the corresponding involvement as shown in the graph. Total number of patients per visit and number of patients without the shown involvement are indicated. ** $p = 0.001$; *** $p < 0.001$.

The overall correlation of tender or swollen DIP joints with NAPSI, either in total or separated for nail bed and nail matrix, across assessment time points was not statistically significant. Similarly, the correlation of PASI, BMI, and disease duration with the course of PsA within the first 3 months was not significant.

3.4. Patient-Reported Outcomes

A substantial impairment of patient QoL was observed before the initiation of treatment with TNF-α inhibitors (mean ± SD DLQI, 12.5 ± 7.4). The QoL significantly improved after 3 months, showing a more than 50% reduction of DLQI compared with baseline (5.9 ± 6.1; $p < 0.001$). Continued treatment led to a further decrease of DLQI until month 24 (mean

± SD DLQI, 4.6 ± 5.7) (Figure 4a). Similarly, patient PsA-associated disability improved 3 months after therapy. Mean ± SD HAQ-DI significantly decreased, from 0.63 ± 0.61 to 0.41 ± 0.55 ($p < 0.001$) and 0.38 ± 0.53 ($p < 0.001$) after 3 and 12 months, respectively, and remained stable and under the cutoff of 0.5 throughout the whole observational period (Figure 4b).

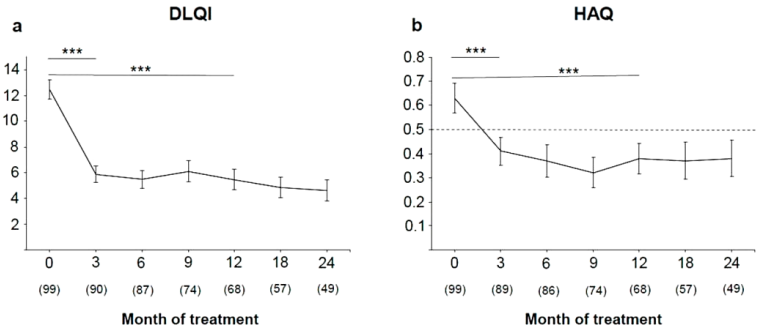

Figure 4. Reduction of (**a**) Dermatological Life Quality Index (DLQI) and (**b**) Health Assessment Questionnaire (HAQ) during therapy. Absolute values of DLQI and HAQ scoring (mean ± SEM) and total number of patients per visit are shown; dashed line represents HAQ 0.5 as functional target for disease control. *** $p < 0.001$.

The number of tender joints significantly correlated with disability. The subgroup of patients with HAQ-DI < 0.5 had a significantly lower number of tender joints than the subgroup with HAQ-DI ≥ 0.5 (Spearman's rho 0.409; Mann–Whitney U test $p < 0.001$).

No significant correlation was observed between nail psoriasis severity (total NAPSI, NAPSI nail bed, and NAPSI nail matrix) and PsA activity (number of tender or swollen joints). Similarly, QoL (DLQI) did not correlate with disability (HAQ-DI).

4. Discussion

In this prospective cohort that included patients with nail psoriasis and PsA from daily clinical practice in a dermatology setting, we investigated the effect of therapy with TNF-α inhibitors over an observational time of 24 months. The indication to treat the endpoints primarily focused on dermatologic aspects and additionally comprised involvement of the joints and patients' disability and QoL.

Dermatologists should evaluate not only the clinical phenotype of psoriasis but also the signs of joint inflammation, comorbidities, imaging, even screening questionnaires for suspicion of PsA, and then determine the need of referral to a rheumatologist [9]. Prompt identification and therapy of patients with Pso at risk to develop PsA is crucial because treatment response after clinical manifestation of PsA is poor [11].

A higher prevalence of PsA has been observed in patients with severe Pso [17]. The mean PASI of the patients included in this study was more than 10, indicating a moderate to severe Pso, which was expected in these dermatology settings. A fast reduction of PASI was observed within 3 months after initiation of the therapy. Because the patients were treated with three different TNF-α inhibitors, including etanercept with slower onset and limited efficacy on Pso, infliximab with fast results after intravenous administration, and adalimumab as gold standard anti–TNF-α therapy for skin and joint involvement [18–20], the PASI rates of the cohort might reflect an average of these three therapies. However, the improvement does not achieve the expected efficacy of newer classes of biologics, such as interleukin (IL)-23 inhibitors [21].

Similarly, nail psoriasis significantly improved within the first three months of treatment, reaching a NAPSI score of approximately 23 and further improved throughout the entire observation time. A recently published study showed similar efficacy on nail

psoriasis in patients with or without PsA treated with adalimumab [22], supporting that TNF-α inhibitors are an efficacious treatment option for nail psoriasis independently of the presence of PsA.

Considered one of the most promising treatments for PsA, TNF-α inhibitors are strongly recommended as the first treatment option if conventional disease modifying drugs are unsuccessful [23]. In this observational study, TNF-α inhibitors were introduced as second-line therapy in patients with Pso with nail and joint involvement. Switch of therapy was mainly based on dermatologic criteria, which could explain the initially moderate PsA activity of the included patients in terms of tender and swollen joints.

Despite having only moderate PsA activity initially, patients showed significant responses to therapy with TNF-α inhibitors during the observational period. According to swollen joint status, low disease activity of PsA was reached after 24 months (mean 76-SJC of 1.8), which is in accordance with current recommendations for the management in PsA [24,25]. A limitation is that for therapy monitoring of PsA, not all parameters for the calculation of minimal disease activity score were considered because this score was not established at the study's onset. However, additional criteria, such as the patient pain visual analog scale (VAS) or the patient global activity VAS, could easily be added to the common questionnaires that patients with PsA receive in the dermatology practice. These additional questions would encourage dermatologists to follow up with patients on disease activity and effectiveness of the PsA treatment in an independent and professional manner in case collaboration with a rheumatologist is not possible.

In this analysis, there was no correlation between NAPSI and affected DIP joint, which was in contrast to previous findings in the cross-sectional study by Lai et al. who found that a significant proportion of patients with radiologically diagnosed PsA had concomitant nail involvement and DIP arthritis [26]. In our study, patients were clinically examined and pre-selected as candidates for systemic treatment with anti-TNFα. As expected, the patients' QoL improved with therapy even after 2 years of continuous therapy. However, the QoL of the patients was still affected, as implied by a mean DLQI score of 4.6 ± 5.7 in Month 24. In a recently published study, DLQI score in patients with PsA was shown to be higher than in patients with psoriasis but without arthritis [27]. An HAQ score below 0.5, as a patient-reported outcome for disability, has been established as a functional target for disease control in rheumatoid arthritis [28], and it is generally accepted as a cutoff of intact ability in other diseases. In this study, patients with PsA treated with a TNF-α inhibitor reached an HAQ score below this limit 3 months after initiation of treatment. The reduction of 0.3 units, the clinically significant decrease [29], was achieved after 9 months of treatment. Patients with PsA report significantly lower scores regarding physical functioning, pain, role limitations, and general health perceptions compared with the general population [30]. TNF-α inhibitors could be a promising therapy for patients with PsA to quickly regain lost functionality.

The scope of this study was to evaluate the effectiveness of TNF-α inhibitors in the real-world dermatology practice, where some dermatologists may lack the expertise to precisely evaluate the disease activity in PsA. To address this deficiency, recruiting sites were advised to keep the same examiner for each patient throughout the observational time to avoid between-rater discrepancies. Additionally, self-explained questionnaires with visualization of PsA examination were provided. Regrettably, enthesitis has not been examined in this study.

Undoubtedly, blocking TNF-α remains a promising target for the treatment of plaque type or nail psoriasis and PsA. In addition, in the interdisciplinary approach of coexisting inflammatory diseases, such as inflammatory bowel disease, hidradenitis suppurativa, or arthritis, TNF-α inhibitors still have a prominent position [31,32]. However, the evolution of new targets for biologics, such as IL-17 or IL-23, or small molecules targeting intracellular signals, have recently revolutionized the spectrum and goals of psoriasis treatment strategies [1,33]. New antibodies against IL-17 or IL-23 have been proven to be effective in PsA, or even axial Spondyloarthritis in the case of anti-IL-17, with a convenient injection schema

and a favorable safety profile [25]. Similar results have been observed in the efficacy of IL-17 and IL-23 antibodies in the treatment of nail psoriasis. Particularly in the long term, the efficacy of all these three classes of biologics, anti-TNFα, anti-IL-17 and anti-IL-23, on nail psoriasis does not seem to differ significantly [34]. A personalized approach should be considered in Pso patients with PsA and nail involvement.

5. Conclusions

TNF-α inhibitors are an efficacious therapy for disease control and improvement of QoL in psoriasis patients with nail psoriasis and concomitant PsA. Dermatologists should regularly monitor psoriasis patients at risk of developing PsA and promptly initiate the appropriate therapy.

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References

1. Ghoreschi, K.; Balato, A.; Enerback, C.; Sabat, R. Therapeutics targeting the IL-23 and IL-17 pathway in psoriasis. *Lancet* **2021**, *397*, 754–766. [CrossRef]
2. Mease, P.; Goffe, B.S. Diagnosis and treatment of psoriatic arthritis. *J. Am. Acad. Dermatol.* **2005**, *52*, 1–19. [CrossRef]
3. Ocampo, D.V.; Gladman, D. Psoriatic arthritis. *F1000Research* **2019**, *8*. [CrossRef]
4. Landeck, L.; Sabat, R.; Ghoreschi, K.; Man, X.Y.; Fuhrmeister, K.; Gonzalez-Martinez, E.; Asadullah, K. Immunotherapy in psoriasis. *Immunotherapy* **2021**, *13*, 605–619. [CrossRef]
5. Nast, A.; Spuls, P.I.; van der Kraaij, G.; Gisondi, P.; Paul, C.; Ormerod, A.D.; Saiag, P.; Smith, C.H.; Dauden, E.; de Jong, E.M.; et al. European S3-Guideline on the systemic treatment of psoriasis vulgaris-Update Apremilast and Secukinumab-EDF in cooperation with EADV and IPC. *J. Eur. Acad. Dermatol. Venereol.* **2017**, *31*, 1951–1963. [CrossRef] [PubMed]
6. Mrowietz, U.; Kragballe, K.; Reich, K.; Spuls, P.; Griffiths, C.E.; Nast, A.; Franke, J.; Antoniou, C.; Arenberger, P.; Balieva, F.; et al. Definition of treatment goals for moderate to severe psoriasis: A European consensus. *Arch. Dermatol. Res.* **2011**, *303*, 1–10. [CrossRef] [PubMed]
7. Ohrndorf, S.; Glimm, A.M.; Ammitzboll-Danielsen, M.; Ostergaard, M.; Burmester, G.R. Fluorescence optical imaging: Ready for prime time? *RMD Open* **2021**, *7*. [CrossRef] [PubMed]
8. Taylor, W.; Gladman, D.; Helliwell, P.; Marchesoni, A.; Mease, P.; Mielants, H.; Group, C.S. Classification criteria for psoriatic arthritis: Development of new criteria from a large international study. *Arthritis Rheumatol.* **2006**, *54*, 2665–2673. [CrossRef] [PubMed]
9. Gisondi, P.; Altomare, G.; Ayala, F.; Conti, A.; Dapavo, P.; De Simone, C.; Foti, C.; Idolazzi, L.; Lubrano, E.; Malara, G.; et al. Consensus on the management of patients with psoriatic arthritis in a dermatology setting. *J. Eur. Acad. Dermatol. Venereol.* **2018**, *32*, 515–528. [CrossRef]
10. Theodorakopoulou, E.; Dalamaga, M.; Katsimbri, P.; Boumpas, D.T.; Papadavid, E. How does the joint dermatology-rheumatology clinic benefit both patients and dermatologists? *Dermatol. Ther.* **2020**, *33*, e13283. [CrossRef] [PubMed]
11. Scher, J.U.; Ogdie, A.; Merola, J.F.; Ritchlin, C. Preventing psoriatic arthritis: Focusing on patients with psoriasis at increased risk of transition. *Nat. Rev. Rheumatol.* **2019**, *15*, 153–166. [CrossRef]
12. Nograles, K.E.; Brasington, R.D.; Bowcock, A.M. New insights into the pathogenesis and genetics of psoriatic arthritis. *Nat. Clin. Pract. Rheumatol.* **2009**, *5*, 83–91. [CrossRef]
13. Ritchlin, C. Navigating the diverse immune landscapes of psoriatic arthritis. *Semin. Immunopathol.* **2021**, *43*, 279–290. [CrossRef]
14. Sabat, R.; Wolk, K.; Loyal, L.; Docke, W.D.; Ghoreschi, K. T cell pathology in skin inflammation. *Semin. Immunopathol.* **2019**, *41*, 359–377. [CrossRef]
15. Blackmore, M.G.; Gladman, D.D.; Husted, J.; Long, J.A.; Farewell, V.T. Measuring health status in psoriatic arthritis: The Health Assessment Questionnaire and its modification. *J. Rheumatol.* **1995**, *22*, 886–893. [PubMed]
16. Bruce, B.; Fries, J.F. The Health Assessment Questionnaire (HAQ). *Clin. Exp. Rheumatol.* **2005**, *23*, S14–S18. [PubMed]
17. Busquets-Perez, N.; Rodriguez-Moreno, J.; Gomez-Vaquero, C.; Nolla-Sole, J.M. Relationship between psoriatic arthritis and moderate-severe psoriasis: Analysis of a series of 166 psoriatic arthritis patients selected from a hospital population. *Clin. Rheumatol.* **2012**, *31*, 139–143. [CrossRef] [PubMed]
18. Chaudhari, U.; Romano, P.; Mulcahy, L.D.; Dooley, L.T.; Baker, D.G.; Gottlieb, A.B. Efficacy and safety of infliximab monotherapy for plaque-type psoriasis: A randomised trial. *Lancet* **2001**, *357*, 1842–1847. [CrossRef]
19. Mease, P.J.; Goffe, B.S.; Metz, J.; VanderStoep, A.; Finck, B.; Burge, D.J. Etanercept in the treatment of psoriatic arthritis and psoriasis: A randomised trial. *Lancet* **2000**, *356*, 385–390. [CrossRef]
20. Menter, A.; Tyring, S.K.; Gordon, K.; Kimball, A.B.; Leonardi, C.L.; Langley, R.G.; Strober, B.E.; Kaul, M.; Gu, Y.; Okun, M.; et al. Adalimumab therapy for moderate to severe psoriasis: A randomized, controlled phase III trial. *J. Am. Acad. Dermatol.* **2008**, *58*, 106–115. [CrossRef] [PubMed]
21. Reich, K.; Gooderham, M.; Thaci, D.; Crowley, J.J.; Ryan, C.; Krueger, J.G.; Tsai, T.F.; Flack, M.; Gu, Y.; Williams, D.A.; et al. Risankizumab compared with adalimumab in patients with moderate-to-severe plaque psoriasis (IMMvent): A randomised, double-blind, active-comparator-controlled phase 3 trial. *Lancet* **2019**, *394*, 576–586. [CrossRef]
22. Kokolakis, G.; Bachmann, F.; Wolk, K.; Sabat, R.; Philipp, S. Efficacy of Adalimumab for Nail Psoriasis During 24 Months of Continuous Therapy. *Acta Derm.-Venereol.* **2020**, *100*, adv00214. [CrossRef]
23. Coates, L.C.; Kavanaugh, A.; Mease, P.J.; Soriano, E.R.; Laura Acosta-Felquer, M.; Armstrong, A.W.; Bautista-Molano, W.; Boehncke, W.H.; Campbell, W.; Cauli, A.; et al. Group for Research and Assessment of Psoriasis and Psoriatic Arthritis 2015 Treatment Recommendations for Psoriatic Arthritis. *Arthritis Rheumatol.* **2016**, *68*, 1060–1071. [CrossRef]
24. Chao, R.; Kavanaugh, A. Psoriatic Arthritis: Newer and Older Therapies. *Curr. Rheumatol. Rep.* **2019**, *21*, 75. [CrossRef]

25. Kerschbaumer, A.; Smolen, J.S.; Dougados, M.; de Wit, M.; Primdahl, J.; McInnes, I.; van der Heijde, D.; Baraliakos, X.; Falzon, L.; Gossec, L. Pharmacological treatment of psoriatic arthritis: A systematic literature research for the 2019 update of the EULAR recommendations for the management of psoriatic arthritis. *Ann. Rheum. Dis.* **2020**, *79*, 778–786. [CrossRef]
26. Lai, T.L.; Pang, H.T.; Cheuk, Y.Y.; Yip, M.L. Psoriatic nail involvement and its relationship with distal interphalangeal joint disease. *Clin. Rheumatol.* **2016**, *35*, 2031–2037. [CrossRef] [PubMed]
27. Langenbruch, A.; Radtke, M.A.; Krensel, M.; Jacobi, A.; Reich, K.; Augustin, M. Nail involvement as a predictor of concomitant psoriatic arthritis in patients with psoriasis. *Br. J. Dermatol.* **2014**, *171*, 1123–1128. [CrossRef] [PubMed]
28. Emery, P.; Kavanaugh, A.; Bao, Y.; Ganguli, A.; Mulani, P. Comprehensive disease control (CDC): What does achieving CDC mean for patients with rheumatoid arthritis? *Ann. Rheum. Dis.* **2015**, *74*, 2165–2174. [CrossRef] [PubMed]
29. Mease, P.J.; Ganguly, R.; Wanke, L.; Yu, E.; Singh, A. How much improvement in functional status is considered important by patients with active psoriatic arthritis: Applying the outcome measures in rheumatoid arthritis clinical trials (OMERACT) group guidelines. *Ann. Rheum. Dis.* **2004**, *63*, 391–392.
30. Tezel, N.; Yilmaz Tasdelen, O.; Bodur, H.; Gul, U.; Kulcu Cakmak, S.; Oguz, I.D.; Karabulut, E. Is the health-related quality of life and functional status of patients with psoriatic arthritis worse than that of patients with psoriasis alone? *Int. J. Rheum. Dis.* **2015**, *18*, 63–69. [CrossRef]
31. Roda, G.; Chien Ng, S.; Kotze, P.G.; Argollo, M.; Panaccione, R.; Spinelli, A.; Kaser, A.; Peyrin-Biroulet, L.; Danese, S. Crohn's disease. *Nat. Rev. Dis. Primers* **2020**, *6*, 22. [CrossRef] [PubMed]
32. Sabat, R.; Jemec, G.B.E.; Matusiak, L.; Kimball, A.B.; Prens, E.; Wolk, K. Hidradenitis suppurativa. *Nat. Rev. Dis. Primers* **2020**, *6*, 18. [CrossRef] [PubMed]
33. Ghoreschi, K.; Gadina, M. Jakpot! New small molecules in autoimmune and inflammatory diseases. *Exp. Dermatol.* **2014**, *23*, 7–11. [CrossRef]
34. Hadeler, E.; Mosca, M.; Hong, J.; Brownstone, N.; Bhutani, T.; Liao, W. Nail Psoriasis: A Review of Effective Therapies and Recommendations for Management. *Dermatol. Ther.* **2021**, *11*, 799–831. [CrossRef] [PubMed]

Efficacy of Adalimumab for Nail Psoriasis During 24 Months of Continuous Therapy

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Kokolakis G, Bachmann F, Wolk K, Sabat R, Philipp S

Im Rahmen der Plaque-Typ Psoriasis ist eine Nagelbeteiligung häufig und tritt bei bis zu 80% der Patient:innen auf. In den meisten Fällen ist ein Therapieansprechen begrenzt. Um die Wirksamkeit von Adalimumab bei der Nagelpsoriasis zu prüfen, erfolgte die Durchführung einer prospektiven, multizentrischen, nicht-interventionellen Studie. In diese Studie erhielten 267 Patient*innen mit Nagelbeteiligung Adalimumab über einen 24-monatigen Zeitraum. Es erfolgte die Bewertung der Wirksamkeit von Adalimumab bei der Nagelbeteiligung der Psoriasis und Prädiktoren für ein besseres therapeutisches Ansprechen wurden festgestellt. Zur statistischen Analyse wurden der Kolmogorov-Smirnov-, Mann-Whitney U-, Wilcoxon-, χ^2-Test sowie die Rangkorrelation nach Spearman angewendet. Eine Reduktion des Nagelbefalles, erfasst mittels Nail Psoriasis Severity Index (NAPSI), um 32.8% nach 3 Monaten ($p < 0.001$) und um fast 50% ($p < 0.001$) nach 6 Monaten verglichen mit mittleren NAPSI-Ausgangswerten von 34.2 ± 1.3 konnte nachgewiesen werden. Nach einem Zeitraum von 6 Monaten erreichten 60.0% der Patient:innen einen NAPSI50, 36.4% der Patient:innen einen NAPSI75, und 21.7% der Patient:innen einen NAPSI90. Nach 12 bzw. 24 Monaten erreichten 42% und 60% der Patient:innen einen NAPSI90 und nach 12 Monaten bestand eine signifikante Korrelation der Verringerung des NAPSI und einer Verbesserung der Lebensqualität, erfasst mit dem Dermatology Life Quality Index. Die Therapie mit Adalimuab zeigte sich effektiver bei jüngeren Patient:innen und Patient:innen mit höherem Body Mass Index (BMI), was eine Stratifizierung nach Alter, Geschlecht und BMI ergab.

Im Rahmen der Studie konnte gezeigt werden, dass Adalimumab eine effektive dauerhafte Therapie bei Nagelbeteiligung der Psoriasis darstellt. Eine Verbesserung der Nagelbeteiligung korreliert mit einer Verbesserung der Hauterkrankung und der krankheitsspezifischen Lebensqualität.

INVESTIGATIVE REPORT

Efficacy of Adalimumab for Nail Psoriasis During 24 Months of Continuous Therapy

Georgios KOKOLAKIS[1,2], Frank BACHMANN[1,3], Kerstin WOLK[1,2,4], Robert SABAT[1,2] and Sandra PHILIPP[1,2]

[1]Psoriasis Research and Treatment Center, [2]Interdisciplinary Group of Molecular Immunopathology and [4]Berlin-Brandenburg Center for Regenerative Therapies, Dermatology/Medical Immunology, Charité-Universitätsmedizin Berlin, and [3]Dermatology Practice Nußbaum und Grunow, Berlin, Germany

Psoriatic nail symptoms are frequent in psoriasis, affecting up to 80% of patients. Therapy responses to nail symptoms are often limited. In this multicentre non-interventional prospective study, 267 patients with nail involvement were treated with adalimumab for a period of 24 months. The efficacy of adalimumab for nail psoriasis was evaluated and predictors for better response were identified. For statistical analysis Kolmogorov-Smirnoff, Mann-Whitney *U*, Wilcoxon, χ^2 and two-tailed Spearman's rank correlation tests were applied. After 3 and 6 months, reductions in Nail Psoriasis Severity Index (NAPSI) of 32.8% ($p < 0.001$) and almost 50% ($p < 0.001$), respectively, were observed, compared with baseline scores (mean NAPSI score, 34.2±1.3). In 6 months, 60.0% of patients achieved NAPSI50, 36.4% NAPSI75, and 21.7% NAPSI90. Approximately 42% and 60% of patients achieved NAPSI90 after 12 and 24 months, respectively. At month 12, reduction in NAPSI significantly correlated with improvement in Dermatological Life Quality Index. Stratification by age, sex, and body mass index indicated that treatment was more effective in younger patients and those with higher body mass index. Adalimumab is an effective long-term therapy for nail psoriasis. The amelioration of nail symptoms correlates with an improvements in the skin disease and quality of life.

Key words: psoriasis; nail psoriasis; nail psoriasis severity index; Dermatology Life Quality Index; adalimumab.

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Corr: Georgios Kokolakis, Psoriasis Research and Treatment Center, Clinic of Dermatology, Venereology and Allergology, Charité-Universitätsmedizin Berlin, Charitéplatz 1, DE-10117 Berlin, Germany. E-mail: georgios.kokolakis@charite.de

SIGNIFICANCE

Adalimumab improves nail psoriasis and the quality of life of patients within 4 months. In this study of 267 patients, a long-term improvement in nail psoriasis maintained over 24 months of therapy was observed. Improvement in nail psoriasis and dermatological quality of life significantly correlate after one year of treatment. Younger patients and patients with a higher body mass index respond better to therapy.

Psoriatic nail symptoms are quite frequent among patients with psoriasis; their prevalence was estimated to be up to 50% (1). Exclusive impairment of the nail unit without cutaneous manifestations of psoriasis is, however, rare and occurs in 1–10% of patients with psoriasis (2). In patients with psoriatic arthritis, nail involvement is more frequent than in patients with plaque psoriasis, as high as 63% (3), and may correlate with more severe disease (4).

The clinical symptoms of nail psoriasis correspond to the involvement of different structures of the nail and can be divided into those in whom the nail matrix is affected and those in whom the nail bed is affected. Pits, transversal or longitudinal ridges, crumbling, leukonychia, as well as red spots in the lunula, are typical symptoms when the nail matrix is involved, and may result in onychorrhexis or complete onychodystrophy. Nail bed involvement is reflected by oil drop spots, subungual hyperkeratosis, onycholysis, and/or splinter haemorrhages (5).

Nail involvement causes psychological distress and feelings of embarrassment; therefore, patients have significant impairment in quality of life. Patients often try to hide their hands or feet (6). Furthermore, approximately half of the affected patients report pain and/or functional disability, resulting in frustration with daily activities in housekeeping or at work (7).

The treatment of nail psoriasis can be challenging, as therapies are often less effective for nail symptoms compared with skin lesions. Topical treatment is limited, since local antipsoriatic agents can only slowly, or sometimes not at all, penetrate the nail plate. Highly concentrated urea, emollients, corticosteroids (either topical or intralesional), calcipotriol, 5-fluorouracil, anthralin, and tazarotene, as well as psoralen plus ultraviolet A (PUVA) phototherapy or dye-pulsed laser, have been proposed as possibly effective local treatments for nail psoriasis, with variable outcomes (8, 9). Regarding systemic treatments, only sparse data are available regarding the efficacy of fumaric acid esters for the treatment of nail psoriasis (10). However, promising results in the treatment of psoriatic nail disease have been reported for methotrexate, acitretin, cyclosporine A, TNF-α blockers, ustekinumab, and, more recently, apremilast, ixekizumab, and secukinumab (11). This cohort study was planned to evaluate nail involvement in patients with plaque psoriasis and the influence of treatment with adalimumab based on real-world data.

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METHODS

Study population, procedures, and treatment regimen

A non-interventional prospective multicentre open-label cohort study was conducted to evaluate the efficacy of adalimumab, etanercept, or infliximab, either as monotherapy or combination therapy on nail psoriasis during 24 months of therapy in patients with moderate to severe plaque psoriasis with or without psoriatic arthritis. Since data with patients under infliximab, etanercept and combination therapies were very limited, only the cohort of patients receiving adalimumab monotherapy was evaluated.

The study population comprised adult patients with moderate to severe psoriasis, as defined by the "rule of ten" (Psoriasis Area and Severity Index (PASI) >10, Dermatological Life Quality Index (DLQI) > 10), who were candidates for systemic treatment with adalimumab according to licensure and had psoriasis of the fingernails. Exclusion criteria were: any other skin diseases that could interfere with the evaluation of psoriatic severity or forms of psoriasis other than plaque-type and the presence of latent or active tuberculosis, hepatitis B and C infection, and HIV infection. Patients who were unable to understand the questionnaires and adhere to the trial procedures were also excluded.

At baseline, adalimumab 80 mg was administered subcutaneously, followed by a dose of 40 mg at week 1 and then 40 mg in regular 2-week intervals over a period of 2 years. All participating patients provided written informed consent. The study was approved by the ethics committee of Charité-Universitätsmedizin Berlin (EA1/236/08) and was conducted according to the principles of the Declaration of Helsinki.

Efficacy assessments

The severity of psoriatic skin alterations was evaluated using PASI score (12) and body surface area (BSA). Nail involvement was estimated using the total Nail Psoriasis Severity Index (NAPSI) score for all fingernails, resulting in scores ranging from 0 to 80 (13). Efficacy assessments were performed at baseline, every 3 months for the first year and then twice annually for the second year of treatment. To minimize the deviation between the examiners, participating study centres were advised to keep the same investigator for each subject throughout the trial. To evaluate the impact of the disease in everyday life, the DLQI questionnaire was used at every scheduled visit (14).

The primary endpoint of the study was the percentage of patients with improvement in nail symptoms as defined by NAPSI75 response (75% improvement compared with baseline) after 12 months. The mean improvement in NAPSI and DLQI after 1-year of continuous treatment with adalimumab was determined as a secondary endpoint of the trial. Nail matrix and nail bed were assessed separately. Furthermore, the efficacy of treatment was also stratified by sex, age, and body mass index (BMI).

Safety

Adverse events, serious adverse events, and pregnancies, as well as abnormal values of routine laboratory parameters and vital signs, were documented throughout the trial. All adverse events, serious adverse events, and pregnancies that occurred during the trial should be reported to the authorities, as appropriate (Bundesinstitut für Arzneimittel und Medizinprodukte).

Statistical analysis

Statistical calculations were made using the Statistical Program for Social Sciences version 22 (IBM, Armonk, NY, USA) and Microsoft Excel 2013 (Microsoft Corporation, Redmond, WA, USA). The values available at each time-point were analysed as observed in a full analysis set without applying "last observation carried forward" method. The Kolmogorov–Smirnov test indicated the absence of normality in the distribution of the parameters. Differences between the non-paired samples of NAPSI improvement stratified according to age, BMI and sex were tested using the Mann–Whitney *U* test. Differences between the paired samples of NAPSI or DLQI improvement over the treatment period were analysed using the Wilcoxon matched-pairs signed-rank test. Differences between frequencies of men and women in NAPSI improvement groups, and NAPSI50 or NAPSI70 responders over the treatment period were tested using a χ^2 test. The correlations between PASI, NAPSI, and DLQI were analysed using a two-tailed Spearman's rank correlation test.

RESULTS

Study population

A total population of 267 patients (184 men; 83 women) with nail psoriasis with or without psoriatic arthritis (plaque psoriasis only, 178; psoriatic arthritis, 89) were included in this multicentre non-interventional prospective cohort trial. Patients had a mean ± standard deviation (SD) age of 47 ± 13.1 years, a BMI of 28.6 ± 5 kg/m^2, PASI score of 17.4 ± 12.5 and a mean ± SD disease duration of 27 ± 12.8 years (**Table I**). Approximately 40% of the included patients reported a family history of psoriasis. All patients were recruited from outpatient departments in Germany.

No significant differences in the severity of nail psoriasis were observed between the groups with lower or higher age or BMI than the mean at baseline. However, male patients had more severe nail psoriasis than female patients (mean NAPSI score, 36.6 vs 29.0; $p=0.01$).

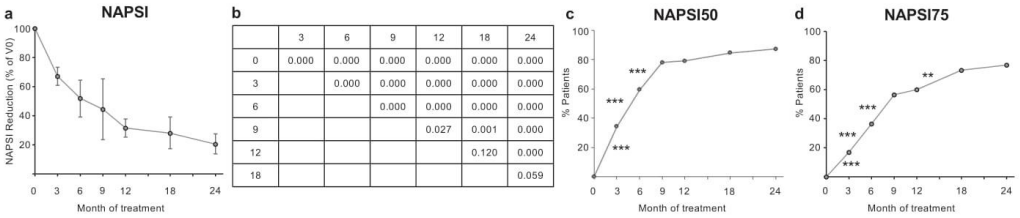
Efficacy of adalimumab on nail involvement

Overall improvement in NAPSI scores during treatment. The impact of adalimumab on nail psoriasis was estimated using the NAPSI, with total scores calculated in addition to nail matrix and nail bed scores. Within 3 months of initiating treatment with adalimumab, patients achieved a statistically significant NAPSI reduction ((32.8 ± 6.2% (mean% ± 95%confidence interval (CI)); $p<0.001$), corresponding to a NAPSI score of 22.9 ± 2.3 (mean ± 95%

Table I. Demographic and clinical characteristics of the study cohort ($n=267$)

Characteristics	Patients
Age, years, mean ± SD	46.8 ± 13.1
Female, %	31.0
Male, %	68.9
BMI, kg/m^2, mean ± SD	28.6 ± 5.3
NAPSI at baseline, mean ± SD	34.2 ± 21.2
PASI at baseline, mean ± SD	17.4 ± 12.5
DLQI at baseline, mean ± SD	12.7 ± 7.7
PsA at baseline, %	33.3
w/o PsA at baseline, %	66.7
Disease duration, years, mean ± SD	27 ± 12.8

SD: standard deviation; BMI: body mass index; NAPSI: Nail Psoriasis Severity Index; PASI: Psoriasis Area and Severity Index; DLQI: Dermatological Life Quality Index; PsA: psoriatic arthritis.



	3	6	9	12	18	24
0	0.000	0.000	0.000	0.000	0.000	0.000
3		0.000	0.000	0.000	0.000	0.000
6			0.000	0.000	0.000	0.000
9				0.027	0.001	0.000
12					0.120	0.000
18						0.059

Fig. 1. Overall improvement in Nail Psoriasis Severity Index (NAPSI), NAPSI50 and NAPSI75 during adalimumab therapy. (a) Percentage reduction in NAPSI compared with baseline (mean ± 95% confidence interval (CI)); (b) *p*-values for NAPSI between time-points; and percentage of patients achieving (c) NAPSI50 and (d) NAPSI75 under therapy with adalimumab. *n*V0=267, *n*V3=240, *n*V6=225, *n*V9=190, *n*V12=187, *n*V18=157, *n*V24=143.

CI), compared with baseline score 34.2 ± 2.5 (mean ± 95% CI) **(Fig. 1)**. Approximately 34% and 17% of the patients achieved NAPSI50 or NAPSI75, respectively, after 3 months of treatment. Parallel improvements in both nail matrix and nail bed scores were observed (**Fig. 2**).

After 6 months, NAPSI was reduced by almost half, 16.2 ± 2.1 (mean ± 95% CI) compared with baseline. A statistically significant improvement between the time-points could be observed until one year after the initiation of the treatment. After a stabilization of nail disease until month 18 of continuous treatment, NAPSI further improved at month 24. At month 6 of treatment, 60% of the treated patients achieved NAPSI50, and 36.4% achieved NAPSI75. Nail bed involvement was dramatically reduced, to 42.2% of the initial score, whereas involvement of the nail matrix was reduced to approximately 55% of baseline values (Fig. 2). Nail bed involvement was further significantly reduced until 18 months after the initiation of treatment. After 1 year, approximately 79% of the patients achieved NAPSI50 and approximately 60% NAPSI75. A total NAPSI improvement of 68.6% was observed (11 ± 2.3 (mean ± 95% CI). NAPSI improvement significantly correlated with improvement in PASI (3.7 ± 1.0 (mean ± 95% CI; correlation coefficient, 0.495; $p < 0.001$). Interestingly, approximately 22%, 42%, and 60% of the patients achieved NAPSI90 after 6, 12, and 24 months of treatment, respectively. In general, nail symptoms continually improved in the first 12 months of treatment and improvement was maintained thorough the 24-month observation period (**Fig. 3**).

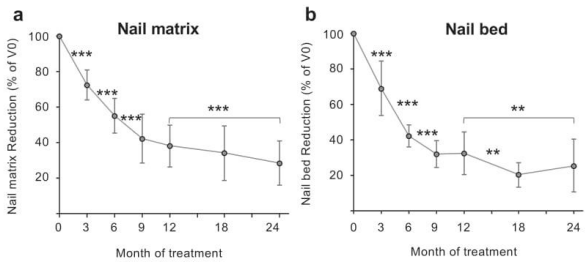


Fig. 2. Nail matrix and nail bed improvement trends during adalimumab therapy. Percentage reduction in (a) nail matrix and (b) nail bed Nail Psoriasis Severity Index scores (mean ± 95% CI). ** $p < 0.01$; *** $p < 0.001$.

Stratification of treatment response by sex, age, and BMI after 12 months

To determine the influence of demographic factors on the efficacy of adalimumab in nail psoriasis, patients were divided into 4 distinct groups according to improvement in nail psoriasis after 1 year of treatment compared with baseline: <50%, 50% to 75%, 75–90%, and 90–100%. Sex, age and BMI were separately examined. In order to identify potential predictors for treatment response, the overall improvement in NAPSI stratified by sex, age, and BMI, and was further analysed in a *post-hoc* manner. Response to treatment did not differ significantly between the 2 sexes, although men had more severe nail disease at baseline. Interestingly, younger patients seemed to respond better to therapy. Overall, at month 12, patients younger than the mean age of the study population had a significantly higher reduction in NAPSI scores than patients >47 years. The mean age of patients with a NAPSI response of 90–100% (mean age, 43.3 ± 1.5 standard error of the mean (SEM) years) was significantly lower compared with those with a <50% NAPSI response (mean age 52.8 ± 2.2 SEM years) or a 50–75% NAPSI response (mean age 50.5 ± 2 SEM years; $p < 0.05$ for both). Surprisingly, patients with NAPSI improvement of 90–100% had significantly higher BMI compared with those with NAPSI response of 50–75% (29.1 ± 0.65 vs 26.8 ± 0.58; $p < 0.05$). However, the overall NAPSI score reduction did not differ significantly between patients with BMIs lower and higher than the mean values (**Fig. 4**).

Impact of adalimumab on patient quality of life

A rapid reduction in DLQI scores was achieved, with a significant improvement (47.5%) compared with baseline ($p < 0.001$), which was apparent within the first 3 months of therapy. After 6 months of treatment, DLQI

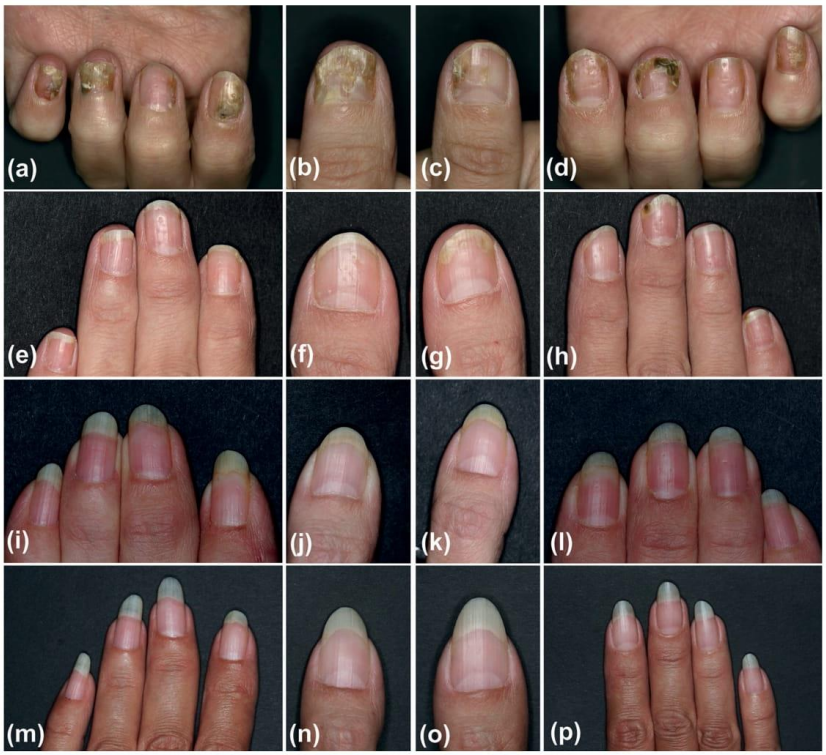


Fig. 3. Clinical outcomes of nail psoriasis in patients under treatment with adalimumab over 24 months. Baseline left (a, b) and right (c, d) hand with severe nail psoriasis. After 3 months of therapy, improvement is noted (e and f, left hand; g and h, right hand). Outcomes further improved after 12 months of treatment (I and j, left hand; k and l, right hand). After 24 months of treatment, no symptoms of nail psoriasis were visible (m and n, left hand; o and p, right hand).

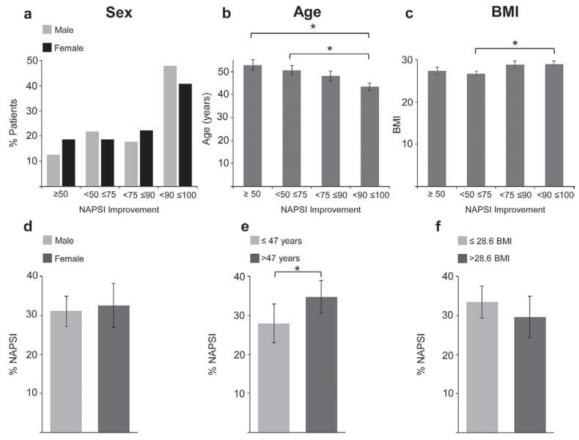


Fig. 4. Stratification of Nail Psoriasis Severity Index (NAPSI) improvement at month 12. Stratification by: (a) sex, (b) age, and (c) body mass index (BMI) of patients achieving an improvement in NAPSI score <50%; 50–75%, 75–90%, and 90–100% (mean±SEM). *$p<0.05$.

further improved, to approximately 40% of the initial visit and was maintained over the observation period. At visit 12, the percentage reduction in DLQI compared with baseline correlated significantly with the improvement in NAPSI (correlation coefficient, 0.343; $p<0.001$; **Fig. 5**).

DISCUSSION

A variety of local and systemic options to treat plaque-type psoriasis is currently available, with well-established strategies, including a wide range of therapeutics (15, 16). However, for the treatment of special subtypes of psoriasis, such as nail psoriasis, the lack of data, as well as restricted therapeutic options, can make treatment quite challenging. In this study, the efficacy of adalimumab was evaluated in a population of 267 patients with psoriatic nail

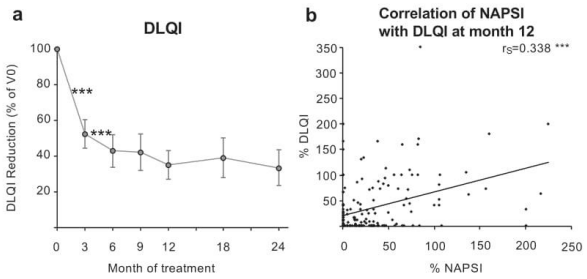


Fig. 5. Dermatology Life Quality Index (DLQI) reduction during adalimumab treatment and correlation with Nail Psoriasis Severity Index (NAPSI) improvement at month 12. (a) Percentage improvement in DLQI scores compared with baseline (mean±95% confidence interval (CI)) and (b) correlation of NAPSI improvement with DLQI improvement after one year of treatment.

disease. All fingernails, not just isolated target nails, were assessed for the duration of the trial.

Conventional systemic therapies have been shown to be efficacious in the treatment of nail psoriasis. In a recently published single-blind randomized trial, methotrexate, at a starting dose of 15 mg/week, was significantly superior to treatment with cyclosporine A, and patients achieved a 43.3% reduction in NAPSI scores after 6 months of treatment compared with 37.2% in the cyclosporine treatment arm (17). However, Reich et al. reported a 36.8% reduction in NAPSI scores after 6 months of treatment with methotrexate 5–25 mg/week (18). Acitretin administered at a dose of 0.2–0.3 mg/kg body weight for 6 months led to a NAPSI reduction of approximately 41% (19). In the case of fumaric acid esters, verified data from trials are unavailable, and the evidence of their efficacy in the treatment of nail psoriasis is based solely on case reports (10). Patients treated with apremilast, the first oral phosphodiesterase 4 inhibitor approved for the treatment of plaque psoriasis, had an improvement of 22.5% in NAPSI response after 16 weeks of treatment (20). NAPSI50 was achieved in 44.6% of patients with apremilast 30 mg twice a day vs 18.7% in the placebo group at week 16 (21).

The introduction of biologics expanded the possibilities for treatment of nail psoriasis. Published data already indicate that adalimumab is effective for the treatment of nail psoriasis. In a subanalysis of the BELIEVE study, the median decrease in NAPSI score was 15.1% and 39.5% at week 8 and 16 compared with baseline scores, respectively (22). A phase 3 randomized placebo-controlled trial especially designed to evaluate the efficacy of adalimumab in nail psoriasis was published during the preparation of this manuscript. At week 16, 20.6% of patients achieved a NAPSI75 response; 26 weeks after the initiation of adalimumab, a NAPSI75 response was achieved in 46.6% of patients (23).

As expected from already published data and clinical experience, in this study, treatment with adalimumab resulted in a rapid improvement in nail psoriasis within 3 months of the initiation of therapy, reaching a reduction of about 55% after 24 weeks. Nail psoriasis continuously improved over 9 and 12 months of treatment. The improvement in symptoms was sustained over 2 years of continuous treatment, during the observation period of the trial. The study population represents real-world patients and was larger than in the phase 3 trial. No differences in terms of age, sex or BMI and severity of nail psoriasis were observed at baseline. Both sexes responded equally after one year of therapy. However, younger patients achieved a more pronounced improvement in nail psoriasis. That could be explained either by the faster growth of nails in younger patients or by the fact that they might have experienced less previous therapies before adalimumab. This finding emphasizes the importance of an earlier initiation of therapy with adalimumab in patients with nail psoriasis. Interestingly, patients with a higher BMI responded better to treatment; even though younger patients were neither obese nor overweight.

In parallel with nail symptoms, the quality of life of patients rapidly improved within the first 3 months of treatment and persisted for the entire duration of the trial. After one year of continuous treatment, improvement in DLQI scores correlated significantly with NAPSI improvement, indicating the impact of nail psoriasis on the quality of life of patients. Interestingly, improvement in PASI also correlated with NAPSI improvement, showing a parallel remission of skin and nail disease after treatment with adalimumab.

Taking into consideration the observed efficacy, as well as the safety profile and the uncomplicated application of the drug, adalimumab appears to be a promising long-term therapeutic option for nail psoriasis. Younger and overweight patients, both high-need groups because of family planning, professional circumstances or metabolic comorbidity, respond better to adalimumab.

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Conflicts of interest: GK has received travel grants or honoraria, or has been a consultant member of advisory boards and speakers

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REFERENCES

1. Langley RG, Dauden E. Treatment and management of psoriasis with nail involvement: a focus on biologic therapy. Dermatology 2010; 221 Suppl 1: 29–42.
2. van der Velden HM, Klaassen KM, van de Kerkhof PC, Pasch MC. Fingernail psoriasis reconsidered: a case-control study. J Am Acad Dermatol 2013; 69: 245–252.
3. Scarpa R, Oriente P, Pucino A, Torella M, Vignone L, Riccio A, et al. Psoriatic arthritis in psoriatic patients. Br J Rheumatol 1984; 23: 246–250.
4. Williamson L, Dalbeth N, Dockerty JL, Gee BC, Weatherall R, Wordsworth BP. Extended report: nail disease in psoriatic arthritis – clinically important, potentially treatable and often overlooked. Rheumatology (Oxford) 2004; 43: 790–794.
5. Jiaravuthisan MM, Sasseville D, Vender RB, Murphy F, Muhn CY. Psoriasis of the nail: anatomy, pathology, clinical presentation, and a review of the literature on therapy. J Am Acad Dermatol 2007; 57: 1–27.
6. Baran R. The burden of nail psoriasis: an introduction. Dermatology 2010; 221 Suppl 1: 1–5.
7. de Jong EM, Seegers BA, Gulinck MK, Boezeman JB, van de Kerkhof PC. Psoriasis of the nails associated with disability in a large number of patients: results of a recent interview with 1,728 patients. Dermatology 1996; 193: 300–303.
8. Radtke MA, Beikert FC, Augustin M. Nail psoriasis – a treatment challenge. J Dtsch Dermatol Ges 2013; 11: 203–219; quiz 220.
9. Treewittayapoom C, Singvahanont P, Chanprapaph K, Haneke E. The effect of different pulse durations in the treatment of nail psoriasis with 595-nm pulsed dye laser: a randomized, double-blind, intrapatient left-to-right study. J Am Acad Dermatol 2012; 66: 807–812.
10. Vlachou C, Berth-Jones J. Nail psoriasis improvement in a patient treated with fumaric acid esters. J Dermatolog Treat 2007; 18: 175–177.
11. Crowley JJ, Weinberg JM, Wu JJ, Robertson AD, Van Voorhees AS, National Psoriasis F. Treatment of nail psoriasis: best practice recommendations from the Medical Board of the National Psoriasis Foundation. JAMA Dermatol 2015; 151: 87–94.
12. Fredriksson T, Pettersson U. Severe psoriasis – oral therapy with a new retinoid. Dermatologica 1978; 157: 238–244.
13. Rich P, Scher RK. Nail Psoriasis Severity Index: a useful tool for evaluation of nail psoriasis. J Am Acad Dermatol 2003; 49: 206–212.
14. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI) – a simple practical measure for routine clinical use. Clin Exp Dermatol 1994; 19: 210–216.
15. Nast A, Boehncke WH, Mrowietz U, Ockenfels HM, Philipp S, Reich K, et al. S3 – Guidelines on the treatment of psoriasis vulgaris (English version). Update. J Dtsch Dermatol Ges 2012; 10 Suppl 2: S1–95.
16. Philipp S, Kokolakis G, Sabat R.Systemische Therapien der Psoriasis und Psoriasisarthritis. Hautarzt 2016; 67: 464–471.
17. Gumusel M, Ozdemir M, Mevlitoglu I, Bodur S. Evaluation of the efficacy of methotrexate and cyclosporine therapies on psoriatic nails: a one-blind, randomized study. J Eur Acad Dermatol Venereol 2011; 25: 1080–1084.
18. Reich K, Langley RG, Papp KA, Ortonne JP, Unnebrink K, Kaul M, et al. A 52-week trial comparing briakinumab with methotrexate in patients with psoriasis. N Engl J Med 2011; 365: 1586–1596.
19. Tosti A, Ricotti C, Romanelli P, Cameli N, Piraccini BM. Evaluation of the efficacy of acitretin therapy for nail psoriasis. Arch Dermatol 2009; 145: 269–271.
20. Papp K, Reich K, Leonardi CL, Kircik L, Chimenti S, Langley RG, et al. Apremilast, an oral phosphodiesterase 4 (PDE4) inhibitor, in patients with moderate to severe plaque psoriasis: Results of a phase III, randomized, controlled trial (Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis [ESTEEM] 1). J Am Acad Dermatol 2015; 73: 37–49.
21. Paul CC, Cather J, Gooderham M, Day R, Mrowietz U, Poulin Y. Apremilast, an oral phosphodiesterase 4 inhibitor, in patients with moderate to severe psoriasis: 16-week results of a phase 3, randomized, controlled trial (ESTEEM 2). J Am Acad Dermatol 2014; 70: AB164.
22. Thaci D, Unnebrink K, Sundaram M, Sood S, Yamaguchi Y. Adalimumab for the treatment of moderate to severe psoriasis: subanalysis of effects on scalp and nails in the BELIEVE study. J Eur Acad Dermatol Venereol 2015; 29: 353–360.
23. Elewski BE, Okun MM, Papp K, Baker CS, Crowley JJ, Guillet G, et al. Adalimumab for nail psoriasis: Efficacy and safety from the first 26 weeks of a phase 3, randomized, placebo-controlled trial. J Am Acad Dermatol 2018; 78: 90–99 e91.

Increased skin clearance and quality of life improvement with brodalumab compared with ustekinumab in psoriasis patients with aggravating lifestyle factors

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Kokolakis G, Vadstrup K, Hansen JB, Carrascosa JM

Bei Patient:innen mit Psoriasis vulgaris treten Adipositas, Alkohol- und Nikotinkonsum häufig auf und sind nachweislich mit einer vermehrten Krankheitsaktivität und einer geringeren Adhärenz sowie einem geringeren Therapieansprechen assoziiert. In der vorliegenden Arbeit wurde die Wirksamkeit des monoklonalen Antikörper gegen den Interleukin (IL)-17-Rezeptor A, Brodalumab, und des monoklonalen Antikörpers gegen die p40 Untereinheit von IL-12 und IL-23, Ustekinumab, im Hinblick auf verschlechternde und möglicherweise die Behandlung beeinflussende Lebensstilfaktoren untersucht. Hierbei erfolgte eine post-hoc-Analyse der zusammengefassten Daten der Phase 3 Studien AMAGINE-2 und -3. In diesen Studien erfolgte die Erfassung des kompletten Rückgangs der Hautveränderungen mittels Psoriasis Area and Severity Index (PASI; PASI100 – Rückgang der Hautveränderungen um 100%) und der Verbesserung der Lebensqualität, welche mittels Dermatology Life Quality Index (DLQI – Ziel-Punktwert: 0/1) eingeschätzt wurde. Zudem erfolgte die Dokumentation bei Vorliegen der Risikofaktoren Adipositas, Alkohol- und Nikotinkonsum. Mittels konkurrierendem Risikomodell der verfügbaren Daten wurde die kumulative Inzidenz eines PASI100 oder eines partielen klinischen Ansprechens über einen Studienzeitraum von 52 Wochen ermittelt. Es wurden 929 Patienten mit moderater bis schwerer Psoriasis (Therapie mit Brodalumab 210mg, n=339; Therapie mit Ustekinumab, n=590) in die vorliegende Studie eingeschlossen. Zum Zeitpunkt der 52. Woche lagen folgende Chancenverhältnisse (95% Konfidenzintervall) für einen kompletten Rückgang der Hautveränderungen unter Therapie mit Brodalumab im Vergleich zur Therapie mit Ustekinumab bei Patienten mit keinem, einem, zwei oder drei Risikofaktoren vor: 2.50 (1.14–5.46, P = 0.0186), 4.64 (2.80–7.69, P<0.0001), 2.06 (1.25–3.40, P = 0.0045), and 2.55 (0.55–11.91, P = 0.2117). Die entsprechenden Chancenverhältnisse (95% Konfidenzintervall) für einen DLQI-Wert von 0/1 betrugen: 1.72 (0.78–3.79, P = 0.1883), 2.49 (1.54–4.02, P<0.0002), 1.57 (0.97–2.54, P = 0.0666), sowie 2.07 (0.45–9.57, P = 0.3438). Insgesamt zeigte sich die kumulative Inzidenz der Patienten:innen, welche einen PASI100 im Zeitraum der 52 Wochen erreichten durchgehend höher in der Brodalumab-Gruppe verglichen mit der Ustekinumab-Gruppe. Dieser Unterschied war unabhängig von der Anzahl der Risikofaktoren (für einen oder zwei vorliegende Risikofaktoren: P<0.0001, für drei vorliegende Risikofaktoren: P=0.0029). Zusammenfassend, führt eine Therapie mit Brodalumab im Vergleich zur Therapie mit Ustekinumab bei moderater bis schwerer Psoriasis zu höheren Raten eines kompletten Rückgangs der Hautveränderungen und einer Normalisierung der

Lebensqualität, wobei die Überlegenheit unabhängig vom Vorliegen von verschlechternden Lebensstil-Faktoren ist.

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ORIGINAL RESEARCH

Increased Skin Clearance and Quality of Life Improvement with Brodalumab Compared with Ustekinumab in Psoriasis Patients with Aggravating Lifestyle Factors

Georgios Kokolakis · Kasper Vadstrup · Jes B. Hansen · Jose Manuel Carrascosa

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ABSTRACT

Introduction: Obesity, smoking, and alcohol consumption are prevalent in psoriasis patients and have been associated with increased disease severity and reduced treatment adherence and response. This post hoc analysis of pooled data from the phase 3 AMAGINE-2 and -3 trials compared the efficacy of brodalumab versus ustekinumab in psoriasis patients with aggravating and potentially treatment-confounding lifestyle risk factors.

Methods: This post hoc analysis evaluated complete skin clearance, as measured by a 100% reduction of Psoriasis Area and Severity Index (PASI100) and quality of life (QoL), as measured by a Dermatology Life Quality Index (DLQI) score of 0/1, by the presence of risk factors (obesity, tobacco or alcohol use). A competing risk model assessed cumulative incidence over 52 weeks with outcomes of PASI100 or inadequate response.

Results: This analysis included 929 patients (brodalumab 210 mg, $n = 339$; ustekinumab, $n = 590$) with moderate-to-severe psoriasis. At week 52, odds ratios (95% confidence intervals [CIs]) for complete clearance with brodalumab versus ustekinumab were 2.50 (1.14–5.46, $P = 0.0186$), 4.64 (2.80–7.69, $P < 0.0001$), 2.06 (1.25–3.40, $P = 0.0045$), and 2.55 (0.55–11.91, $P = 0.2117$) in patients with no, one, two, or three risk factors, respectively. Corresponding odds ratios (ORs) (95% CIs) for DLQI 0/1 with brodalumab versus ustekinumab were 1.72 (0.78–3.79, $P = 0.1883$), 2.49 (1.54–4.02, $P < 0.0002$), 1.57 (0.97–2.54, $P = 0.0666$), and 2.07 (0.45–9.57, $P = 0.3438$). The 52-week cumulative incidence of patients achieving PASI100 was consistently higher for brodalumab versus ustekinumab, regardless of number of risk factors ($P < 0.0001$ for one or two risk factors and $P = 0.0029$ for three risk factors).

Conclusions: Higher levels of complete skin clearance and QoL were achieved and maintained with brodalumab versus ustekinumab in patients with moderate-to-severe psoriasis, regardless of the presence of lifestyle risk factors.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13555-021-00618-5.

G. Kokolakis (✉)
Clinic of Dermatology, Venereology and Allergology, Psoriasis Research and Treatment Centre, Charité—Universitätsmedizin Berlin, Luisenstrasse 2, 10117 Berlin, Germany
e-mail: Georgios.kokolakis@charite.de

K. Vadstrup · J. B. Hansen
LEO Pharma A/S, Industriparken 55, 2750 Ballerup, Denmark

J. M. Carrascosa
Department of Dermatology, Hospital Universitari Germans Trias i Pujol, Universitat Autònoma of Barcelona, IGTP, Carretera de Canyet, s/n, 08916 Badalona, Barcelona, Spain

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Why carry out this study?

Obesity, smoking, and alcohol consumption are prevalent in patients with psoriasis.

These lifestyle risk factors have been associated with increased psoriasis severity, limited systemic treatment options, and reduced treatment response.

This analysis compared the efficacy of brodalumab versus ustekinumab in patients with moderate-to-severe psoriasis with or without the presence of at least one of these three aggravating lifestyle risk factors at baseline.

What was learned from the study?

This post hoc analysis of pooled data from the phase 3 AMAGINE-2 and -3 trials found higher levels of complete skin clearance and quality of life were achieved and maintained with brodalumab versus ustekinumab in patients with moderate-to-severe psoriasis, regardless of the presence of lifestyle risk factors.

Brodalumab may offer a good treatment option for psoriasis patients who have a history of aggravating lifestyle risk factors.

INTRODUCTION

Psoriasis is a chronic inflammatory skin disease with systemic manifestations that has a substantial impact on quality of life (QoL) [1, 2]. While the influence of genetics in psoriasis is well established [3], the extent to which exogenous lifestyle factors such as smoking, alcohol intake, and body mass index (BMI) influence psoriasis pathogenesis is less clear [4].

Alcohol misuse is common in patients with moderate-to-severe psoriasis [approximately > 10% body surface area (BSA) involvement] [5, 6]. Some patients may use alcohol to manage their psychological distress [5], and a correlation between increased alcohol intake and extent of BSA involvement by psoriasis has been shown [5, 6]. Alcohol use has also been linked to the triggering/worsening of psoriasis and poor response to treatment [7].

Evidence suggests that smoking affects the onset of psoriasis [8, 9]. Nicotine also stimulates innate immune cells, including dendritic cells, macrophages, and keratinocytes, which play key roles in the pathogenesis of psoriasis [8]. Random-effects meta-analysis of 25 prevalence studies identified associations between psoriasis and current smoking, and between psoriasis and former smoking [9]. Three incidence studies showed an association between smoking and the incidence of psoriasis, with a possible dose–effect of smoking intensity and duration on psoriasis incidence [9]. Furthermore, smoking has been linked to the clinical severity of psoriasis and response to treatment [10, 11]. Importantly, there is evidence to suggest that smoking may also negatively impact treatment adherence [12, 13]. A systematic review of treatment adherence in patients with psoriasis assessed the role of smoking and identified two studies that reported greater adherence among non-smokers compared with smokers, while a third study reported no association [12]. More recently, registry data have shown being a current smoker to be a predictor of biologic discontinuation [13].

Meta-analyses have shown that higher BMI and obesity are risk factors for psoriasis [14]. In addition, obesity, defined by the World Health Organization as a BMI of 30 kg/m^2 or above [15], is associated with more severe psoriasis [14].

Moderate-to-severe psoriasis is increasingly treated with biologics that target various cytokines responsible for psoriasis evolution, including interleukin (IL)-17, IL-23, and tumor

necrosis factor (TNF)-α [16, 17]. While biologics are effective for many patients in the short term [18], some patients fail to respond and 13% of patients discontinue treatment within the first year because of ineffectiveness [13]. Furthermore, as the efficacy of these agents may be negatively impacted by lifestyle factors [17], it is important that lifestyle risk factors are screened for and considered when selecting psoriasis medication [19].

Brodalumab is a fully human monoclonal antibody that binds with high affinity to the IL-17 receptor subunit A (IL-17RA) [20]. By binding to IL-17RA, brodalumab inhibits downstream signaling of multiple IL-17 family cytokines involved in the pathogenesis of psoriasis [20], in contrast to biologics such as secukinumab and ixekizumab, which specifically target IL-17A [21, 22]. In phase 3 trials in patients with moderate-to-severe psoriasis, brodalumab provided high levels of skin clearance for up to 52 weeks [23, 24].

In this post hoc analysis, we evaluated skin clearance and impact on patient QoL over 52 weeks in the phase 3 AMAGINE-2 and -3 studies according to the presence of obesity, tobacco use, and alcohol use. The aims were to compare the efficacy of brodalumab versus ustekinumab in patients with psoriasis with aggravating lifestyle risk factors and to identify lifestyle risk factors that could affect response to therapy.

METHODS

Study Design and Patients

Data were pooled from two phase 3, randomized, double-blind, placebo- and ustekinumab-controlled, 52-week studies of brodalumab (AMAGINE-2 [NCT01708603] and AMAGINE-3 [NCT01708629]). The AMAGINE-2 and -3 study designs have previously been described [24] and are provided in Supplementary Fig. 1. In brief, patients aged ≥ 18 years with moderate-to-severe plaque psoriasis (defined as a Psoriasis Area and Severity Index [PASI] score ≥ 12, static Physician's Global Assessment [sPGA] score of ≥ 3 and ≥ 10% BSA involvement of ≥ 6 months duration) were enrolled in the trials. Patients were randomized 2:2:1:1 to receive brodalumab 210 mg, brodalumab 140 mg, or placebo on day 1 and weeks 1, 2, 4, 6, 8 and 10; or ustekinumab (45 mg for patients ≤100 kg and 90 mg for patients > 100 kg) on day 1, week 4 and every 12 weeks (Q12W) thereafter. At week 12, brodalumab patients were re-randomized 2:2:2:1 to receive a brodalumab maintenance dose of 210 mg every 2 weeks (Q2W) or 140 mg Q2W every 4 weeks (Q4W) or every 8 weeks (Q8W). Ustekinumab patients continued to receive ustekinumab Q12W, and placebo patients received 210 mg of brodalumab Q2W.

Patients were eligible for rescue treatment with brodalumab 210 mg Q2W if they had an inadequate response (defined as sPGA ≥ 3 or persistent values of 2 over a ≥ 4-week period at, or after, week 16). Rescue treatment was blinded. At week 16, all patients with an inadequate response received rescue treatment with brodalumab 210 mg. After week 16 and through week 52, brodalumab patients were rescued with brodalumab 210 mg Q2W while ustekinumab patients continued to receive ustekinumab. After receiving rescue treatment for ≥ 12 weeks, patients were assessed and discontinued if they were non-responders.

The study protocols were approved by the institutional review boards at each participating center, and the studies were conducted in accordance with the International Conference on Harmonization guideline for Good Clinical Practice, the Declaration of Helsinki, and the Health Insurance Portability and Accountability Act of 1996 or relevant regional regulations. All subjects provided informed consent to participate in the study.

Assessments

Lifestyle Risk Factors

Tobacco and alcohol use were self reported. Patients were categorized as "yes" (current user or stopped within the last year) or "no" (former user/no use). Patients were categorized as obese if they had a BMI of ≥ 30 kg/m^2.

Table 1 Demographic and baseline characteristics

Characteristic	No risk factors		One risk factor		Two risk factors		Three risk factors	
	Brodalumab (n = 51)	Ustekinumab (n = 76)	Brodalumab (n = 140)	Ustekinumab (n = 221)	Brodalumab (n = 122)	Ustekinumab (n = 236)	Brodalumab (n = 26)	Ustekinumab (n = 57)
Male, n (%)	34 (66.7)	48 (63.2)	93 (66.4)	144 (65.2)	82 (67.2)	170 (72.0)	21 (80.8)	42 (73.7)
Age, years	47.2 (14.7)	40.8 (13.9)	44.7 (13.4)	45.9 (12.9)	43.3 (13.2)	46.4 (12.7)	44.3 (11.9)	42.6 (12.6)
Weight, kg	75.5 (10.8)	75.8 (12.0)	88.0 (23.9)	85.7 (19.8)	96.7 (26.9)	96.9 (23.8)	102.5 (12.3)	107.5 (23.3)
BMI, kg/m^2	25.7 (2.8)	25.6 (2.7)	29.6 (7.7)	29.3 (6.4)	32.0 (8.2)	32.2 (7.6)	34.0 (3.1)	35.3 (5.4)
White, n (%)	48 (94.1)	64 (84.2)	127 (90.7)	200 (90.5)	110 (90.2)	216 (91.5)	23 (88.5)	52 (91.2)
Duration of disease, years	17.4 (10.6)	18.7 (13.2)	18.0 (12.0)	18.5 (11.8)	16.9 (12.0)	19.0 (12.6)	15.2 (11.7)	17.6 (11.1)
BSA, %	26.5 (14.2)	29.8 (18.9)	27.6 (16.0)	27.1 (18.6)	27.3 (17.4)	27.7 (18.8)	23.6 (15.6)	25.9 (17.7)
PASI score	20.7 (8.4)	20.2 (8.3)	20.2 (7.2)	20.0 (8.3)	20.8 (8.5)	20.0 (8.5)	19.2 (7.3)	20.1 (8.2)
DLQI score	16.2 (6.5)	15.8 (7.1)	14.4 (7.3)	14.6 (7.5)	14.9 (7.7)	14.7 (7.1)	13.8 (6.4)	15.6 (7.4)
NAPSI score	8.4 (3.3)	7.9 (3.3)	9.4 (3.2)	9.9 (3.4)	9.5 (4.3)	9.9 (3.6)	9.7 (2.9)	11.4 (3.8)
sPGA score	3.4 (0.6)	3.5 (0.6)	3.4 (0.6)	3.5 (0.6)	3.6 (0.6)	3.5 (0.6)	3.6 (0.6)	3.6 (0.6)
PSI score	19.6 (7.2)	18.6 (7.1)	18.4 (6.9)	18.4 (7.1)	19.6 (7.4)	18.5 (6.7)	18.8 (5.6)	20.5 (6.3)

Data are mean (SD) unless otherwise stated

BMI body mass index, *BSA* body surface area, *DLQI* Dermatology Life Quality Index, *n* number of patients, *NAPSI* Nail Psoriasis Severity Index, *PASI* Psoriasis Area and Severity Index, *PSI* Psoriasis Symptom Inventory, *SD* standard deviation, *sPGA* static Physician's Global Assessment

Table 2 Distribution of lifestyle factors at baseline, by treatment

Lifestyle risk factor, *n* (%)	Brodalumab (*n* = 339)	Ustekinumab (*n* = 590)
None	51 (15.0)	76 (12.9)
1	140 (41.3)	221 (37.5)
2	122 (36.0)	236 (40.0)
3	26 (7.7)	57 (9.7)

	Brodalumab (*n* = 339)		Ustekinumab (*n* = 590)	
	Yes	No	Yes	No
Alcohol (current or stopped within last year)	201 (59.3)	138 (40.7)	383 (64.9)	207 (35.1)
Smoking (current or stopped within last year)	111 (32.7)	228 (67.3)	209 (35.4)	381 (64.6)
Obesity (BMI $\geq$ 30 kg/m^2)	147 (43.4)	192 (56.6)	271 (45.9)	319 (54.1)
Weight > 100 kg	93 (27.4)	246 (72.6)	166 (28.1)	424 (71.9)

BMI body mass index, *n* number of patients

Disease Severity, Response, and QoL

Disease severity was evaluated using three instruments: the PASI, the Psoriasis Symptom Inventory (PSI), and the sPGA. The PASI is the most commonly used tool for measuring disease activity and treatment effect in clinical trials of biologics to treat psoriasis. While PASI75 (a 75% reduction in the PASI score with respect to baseline) has historically been considered the treatment goal for moderate-to-severe psoriasis [25], studies of newer biologics have included PASI90 and PASI100 as endpoints [23, 24, 26–30]. Patients who achieve PASI100 are more likely to have improved QoL scores and a reduction in the signs and symptoms of psoriasis [24, 31].

The PSI is a patient-reported outcome instrument (developed by Amgen) that measures the severity of psoriasis signs and symptoms. The eight-point questionnaire assesses signs and symptoms of itch, redness, scaling, burning, stinging, cracking, flaking, and pain. Each item is scored on a scale of 0 (not at all severe) to 4 (very severe), giving a total score ranging from 0 (best) to 32 (worst). Response on the PSI is defined as attaining a total score of $\leq$ 8, with each symptom rated as either 0 (not at all severe) or 1 (mild) [32]. The sPGA, which assesses erythema, induration, and scaling on a scale from 0 to 5, where 0 indicates clear and 5 indicates severe disease [33], was also used to measure response to treatment. QoL was assessed using the Dermatology Life Quality Index (DLQI). A DLQI score of 0 or 1 indicates no effect at all on patient's life [34]. PASI, PSI, and DLQI scores were measured at least once every 2–4 weeks throughout the trials.

Responder Analyses for Clearance (PASI100), DLQI 0/1, and PSI ≤ 8 at a Given Time Point by Risk Factor History

This analysis included data from patients randomized to receive constant dosing of either the approved dose of brodalumab (210 mg Q2W) or ustekinumab for the entire 52-week treatment period, subdivided according to risk factor history (none, one risk factor, two risk factors, or three risk factors).

Proportions of patients achieving PASI100, PSI $\leq$ 8 responder status, and DLQI 0/1 are presented according to risk factor history and visit (weeks 0–52 for PASI100 and DLQI 0/1; weeks 0–24 and 48–52 for PSI $\leq$ 8 responder),

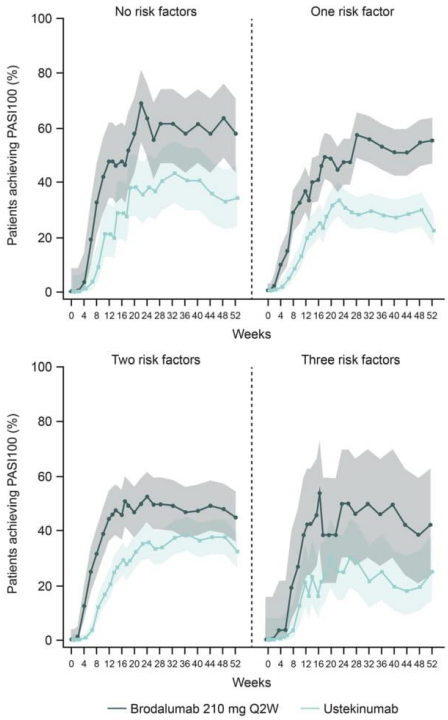


Fig. 1 Percentage of patients achieving PASI100, by visit, treatment, and history of lifestyle risk factors. Pooled data from the AMAGINE-2 and -3 trials. Shading indicates 95% confidence interval. *PASI* Psoriasis Area and Severity Index, *Q2W* every 2 weeks

with comparisons between treatment groups reported as odds ratios (ORs) and 95% confidence intervals (95% CIs) calculated using the Cochran–Mantel–Haenszel method and adjusted for study, baseline total body weight group (≤ 100 or > 100 kg), geographic region, and within-study and subgroup baseline score ($\leq$ or $>$ median). Non-responder imputation was used to handle missing data.

Competing Risk Model by Risk Factor History

The cumulative incidence of complete clearance over 52 weeks was analyzed by risk factor history using a competing risk model [35] with the outcomes of:

(a) Achieving PASI100, or
(b) Inadequate response (defined as sPGA ≥ 3, or sPGA ≥ 2 for > 4 weeks at or after week 16)

Comparisons between treatment arms were performed using subdistribution hazard ratios and associated chi-squared tests [36, 37] and adjusted for baseline characteristics, as detailed for the responder analyses.

RESULTS

Patients

A total of 929 patients (brodalumab 210 mg, $n = 339$; ustekinumab, $n = 590$) were included in this analysis. Baseline characteristics were generally balanced across treatment and risk groups (Table 1). Baseline PASI, PSI, and DLQI scores were similar across the subgroups.

Lifestyle Risk Factors

At baseline, approximately 85% of patients had a history of one or more lifestyle risk factors. In the brodalumab and ustekinumab groups, respectively, 41.3% and 37.5% had a history of one risk factor, 36.0% and 40.0% had a history of two risk factors, and 7.7% and 9.7% had a history of three risk factors (Table 2).

Alcohol use was the most common risk factor: 59.3% and 64.9% of patients in the brodalumab and ustekinumab groups, respectively, had a history of alcohol use. Almost half of the patients in both groups were obese (43.4% and 45.9% in the brodalumab and ustekinumab groups, respectively, Table 2). Further details of tobacco and alcohol use (i.e., light, moderate, or heavy use) are provided in Supplementary Table 1.

Table 3 Overview of patients with PASI100, PSI response, and DLQI 0/1 at weeks 12 and 52, according to lifestyle risk factors and treatment

	No risk factors			One risk factor			Two risk factors			Three risk factors		
	Brodalumab (n = 51)	Ustekinumab (n = 76)	OR (95% CI)	Brodalumab (n = 140)	Ustekinumab (n = 221)	OR (95% CI)	Brodalumab (n = 122)	Ustekinumab (n = 236)	OR (95% CI)	Brodalumab (n = 26)	Ustekinumab (n = 57)	OR (95% CI)
PASI100 week 12	24 (47.1)	16 (21.1)	3.54 (1.41–8.87)**	51 (36.4)	44 (19.9)	2.54 (1.52–4.25)***	56 (45.9)	49 (20.8)	3.59 (2.09–6.17)***	10 (38.5)	12 (21.1)	1.53 (0.45–5.22)
PASI100 week 52	29 (56.9)	26 (34.2)	2.50 (1.14–5.46)*	77 (55.0)	49 (22.2)	4.64 (2.80–7.69)***	56 (45.9)	76 (32.2)	2.06 (1.25–3.40)**	11 (42.3)	15 (26.3)	2.55 (0.55–11.91)
PSI response week 12	37 (72.5)	47 (61.8)	2.11 (0.80–5.53)	89 (63.6)	117 (52.9)	1.57 (0.95–2.60)	76 (62.3)	134 (56.8)	1.11 (0.66–1.88)	20 (76.9)	30 (52.6)	2.37 (0.62–9.03)
PSI response week 52	23 (45.1)	36 (47.4)	1.09 (0.48–2.43)	70 (50.0)	69 (31.2)	2.56 (1.55–4.22)***	57 (46.7)	100 (42.4)	1.45 (0.86–2.45)	10 (38.5)	23 (40.4)	1.03 (0.28–3.85)
DLQI 0/1 week 12	30 (58.8)	36 (47.4)	1.75 (0.75–4.10)	84 (60.0)	89 (40.3)	2.20 (1.37–3.54)***	69 (56.6)	120 (50.8)	1.14 (0.71–1.81)	20 (76.9)	24 (42.1)	3.54 (0.84–14.92)
DLQI 0/1 week 52	32 (62.7)	36 (47.4)	1.72 (0.78–3.79)	76 (54.3)	73 (33.0)	2.49 (1.54–4.02)***	67 (54.9)	108 (45.8)	1.57 (0.97–2.54)	11 (42.3)	18 (31.6)	2.07 (0.45–9.57)

All data are n (%); ORs are brodalumab versus ustekinumab

CI confidence interval, *DLQI* Dermatology Life Quality Index, *n* number of patients, *OR* odds ratio, *PASI* Psoriasis Area and Severity Index, *PSI* Psoriasis Symptom Inventory

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$

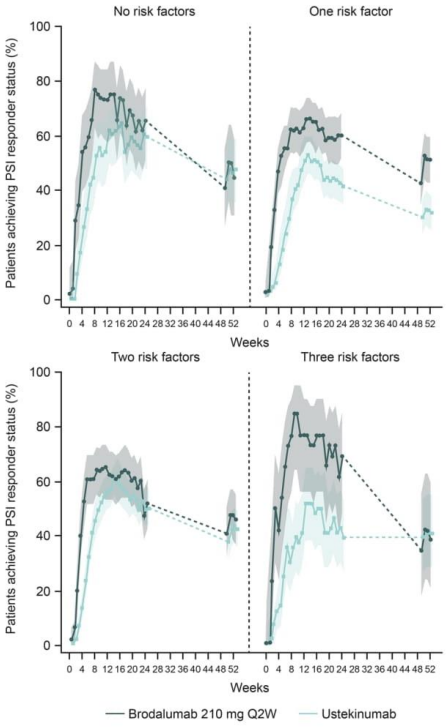


Fig. 2 Percentage of patients achieving PSI responder status (≤ 8) by visit, treatment, and history of lifestyle risk factors. Pooled data from the AMAGINE-2 and -3 trials. Shading indicates 95% confidence interval. Data were not collected between weeks 24 and 48; indicated by a broken line. *PSI* Psoriasis Symptom Inventory, *Q2W* every 2 weeks

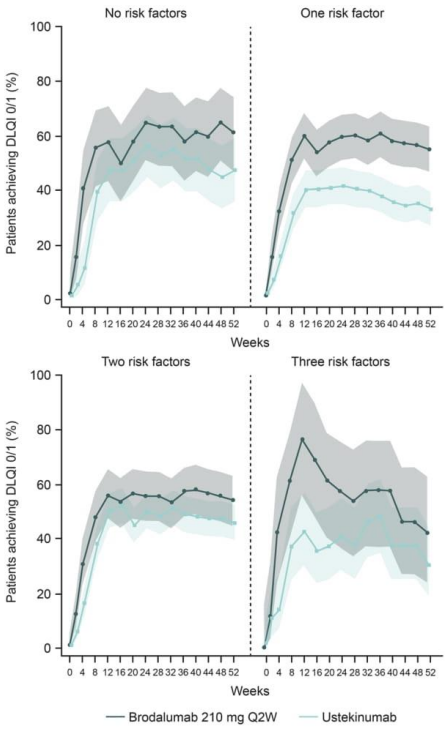
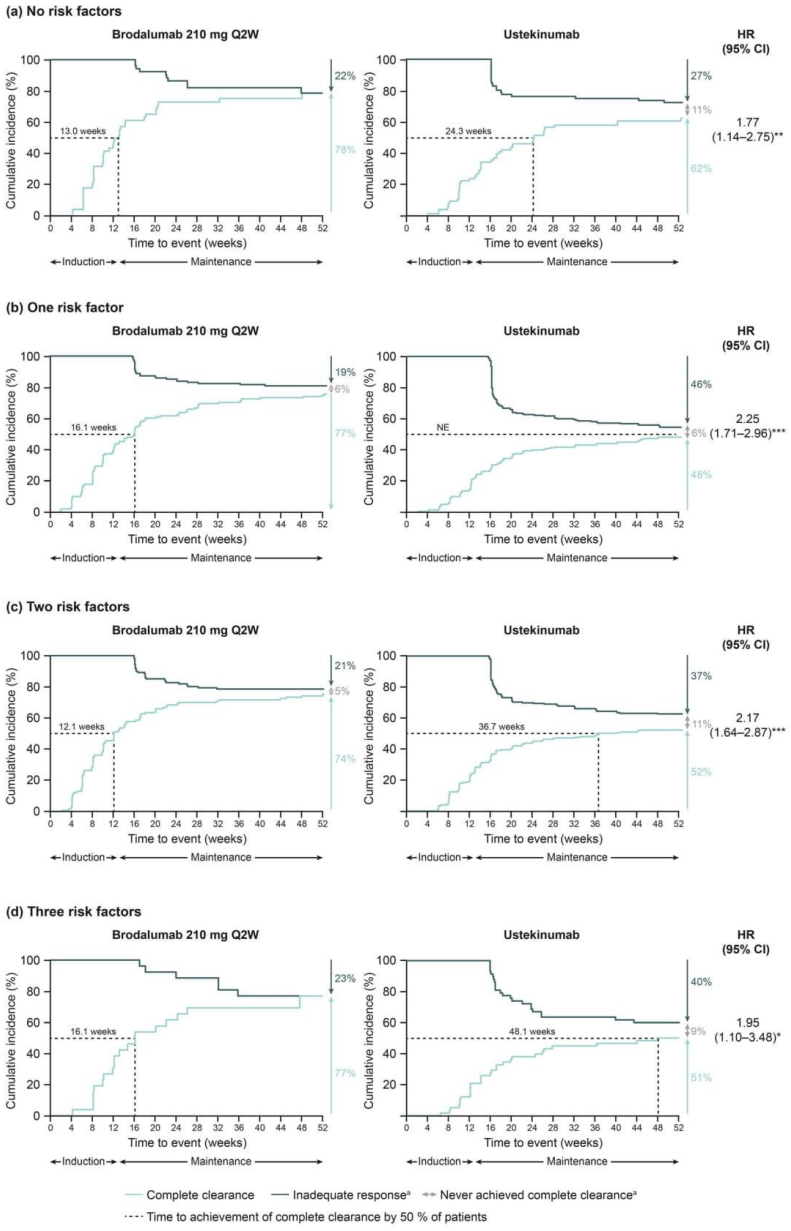


Fig. 3 Percentage of patients with DLQI 0/1 by visit, treatment, and history of lifestyle risk factors. Pooled data from the AMAGINE-2 and -3 trials. Shading indicates 95% confidence interval. *DLQI* Dermatology Life Quality Index, *Q2W* every 2 weeks

Responder Analysis for Complete Clearance (PASI100), PSI ≤ 8, and DLQI 0/1 by Number of Lifestyle Risk Factors

Regardless of the presence of risk factors, brodalumab treatment was associated with earlier achievement of complete clearance and consistently higher proportions of complete clearance versus ustekinumab (Fig. 1); differences between the brodalumab and ustekinumab groups were statistically significant for subgroups with no, one, or two baseline risk factors, but did not reach statistical significance in the subgroup with three risk factors. At week 12, PASI100 was achieved by 47.1% of patients on brodalumab versus 21.1% on ustekinumab with no risk factors (OR 3.54, 95% CI 1.41–8.87, $P = 0.0073$), 36.4% versus 19.9% with one risk factor (OR 2.54, 95% CI 1.52–4.25, $P = 0.0004$), 45.9% versus 20.8% with two risk factors (OR 3.59, 95% CI 2.09–6.17, $P < 0.0001$), and 38.5% versus 21.1% with three risk factors (OR 1.53, 95% CI 0.45–5.22, $P = 0.5127$) (Fig. 1, Table 3). At week 52, the proportions of patients in the brodalumab and ustekinumab groups achieving complete clearance were 56.9% versus 34.2% (OR 2.50, 95% CI 1.14–5.46, $P = 0.0186$), 55.0%


(a) No risk factors
Brodalumab 210 mg Q2W
Ustekinumab
HR (95% CI)
Cumulative incidence (%)
13.0 weeks
24.3 weeks
22%
78%
27%
11%
62%
1.77 (1.14–2.75)**
Time to event (weeks)
Induction
Maintenance
(b) One risk factor
16.1 weeks
NE
19%
6%
77%
46%
6%
48%
2.25 (1.71–2.96)***
(c) Two risk factors
12.1 weeks
36.7 weeks
21%
5%
74%
37%
11%
52%
2.17 (1.64–2.87)***
(d) Three risk factors
16.1 weeks
48.1 weeks
23%
77%
40%
9%
51%
1.95 (1.10–3.48)*
Complete clearance
Inadequate response[a]
Never achieved complete clearance[a]
Time to achievement of complete clearance by 50 % of patients

◀**Fig. 4** Cumulative incidence of patients achieving PASI100 by visit, treatment, and history of lifestyle risk factors (competing risk analysis). *$P < 0.05$; **$P < 0.01$; ***$P < 0.0001$. [a]Defined as static Physician's Global Assessment ≥ 3 or persistent values of 2 over at least a 4-week period or after week 16. *CI* confidence interval, *HR* hazard ratio, *NE* not estimable, *PASI* Psoriasis Area and Severity Index, *Q2W* every 2 weeks

versus 22.2% (OR 4.64, 95% CI 2.80–7.69, $P < 0.0001$), 45.9% versus 32.2% (OR 2.06, 95% CI 1.25–3.40, $P = 0.0045$), and 42.3% versus 26.3% (OR 2.55, 95% CI 0.55–11.91, $P = 0.2117$) in the corresponding risk factor groups, respectively.

More patients achieved a PSI response (total PSI ≤ 8) with brodalumab treatment versus ustekinumab, regardless of risk factor history, at week 12 (Fig. 2). At week 12, 72.5% of patients on brodalumab versus 61.8% on ustekinumab with no risk factors (OR 2.11, 95% CI 0.80–5.53, $P = 0.1252$), 63.6% versus 52.9% with one risk factor (OR 1.57, 95% CI 0.95–2.60, $P = 0.0742$), 62.3% versus 56.8% with two risk factors (OR 1.11, 95% CI 0.66–1.88, $P = 0.6979$), and 76.9% versus 52.6% with three risk factors (OR 2.37, 95% CI 0.62–9.03, $P = 0.2091$) achieved a PSI response (Table 3).

Higher proportions of patients in the brodalumab group achieved DLQI 0/1 compared with the ustekinumab group, independent of baseline risk factors (Fig. 3). At week 12, 58.8% of patients on brodalumab versus 47.4% on ustekinumab with no risk factors (OR 1.75, 95% CI 0.75–4.10, $P = 0.2082$), 60.0% versus 40.3% with one risk factor (OR 2.20, 95% CI 1.37–3.54, $P = 0.0006$), 56.6% versus 50.8% with two risk factors (OR 1.14, 95% CI 0.71–1.81, $P = 0.5905$), and 76.9% versus 42.1% with three risk factors (OR 3.54, 95% CI 0.84–14.92, $P = 0.0608$) achieved DLQI 0/1 (Table 3). At week 52, the proportions of patients in the brodalumab and ustekinumab groups achieving DLQI 0/1 were 62.7% versus 47.4% (OR 1.72, 95% CI 0.78–3.79, $P = 0.1883$), 54.3% versus 33.0% (OR 2.49, 95% CI 1.54–4.02, $P = 0.0002$), 54.9% versus 45.8% (OR 1.57, 95% CI 0.97–2.54, $P = 0.0666$), and 42.3% versus 31.6% (OR 2.07, 95% CI 0.45–9.57, $P = 0.3438$) in the corresponding risk factor groups.

Competing Risk Model by Number of Risk Factors

The 52-week cumulative incidence of patients achieving PASI100 was higher for brodalumab versus ustekinumab regardless of the number of risk factors ($P < 0.0001$ for one and two risk factors; $P = 0.0229$ for three risk factors; Fig. 4).

The median time to achievement of PASI100 in brodalumab patients was not affected by baseline risk factors (Fig. 4). The median time to achieve complete clearance could not be estimated for ustekinumab patients in the one risk factor subgroup, as fewer than 50% of patients achieved complete clearance by week 52.

Responder Analysis for Complete Clearance and DLQI 0/1 by Visit by Various Lifestyle Risk Factors

A higher proportion of brodalumab-treated patients achieved PASI100 in each subgroup through week 52, independent of risk factor (Fig. 5). The ORs (95% CIs) for complete clearance with brodalumab versus ustekinumab at week 52 were: smoking OR 3.59 (2.47–5.20, $P < 0.0001$), alcohol use OR 2.87 (1.75–4.71, $P < 0.0001$), and obesity OR 3.44 (2.33–5.07, $P < 0.0001$). Similarly, a higher proportion of patients in the brodalumab group achieved DLQI 0/1 (Fig. 5) or a PSI response (data not shown) in each risk factor subgroup through week 52. Figure 6 compares ORs and 95% CIs for achieving complete clearance and DLQI 0/1 at weeks 12 and 52, by lifestyle risk factors.

DISCUSSION

Obesity, smoking, and alcohol use are lifestyle risk factors associated with increased psoriasis severity, limited systemic treatment options, and reduced treatment response [6, 7, 10–12, 15]. Obesity may predict biologic treatment discontinuation and lead to lower efficacy of anti-TNF-α agents [15, 38]. Smoking and obesity have been associated with non-response to anti-TNF-α therapies, and in a retrospective study of 110 patients with psoriasis

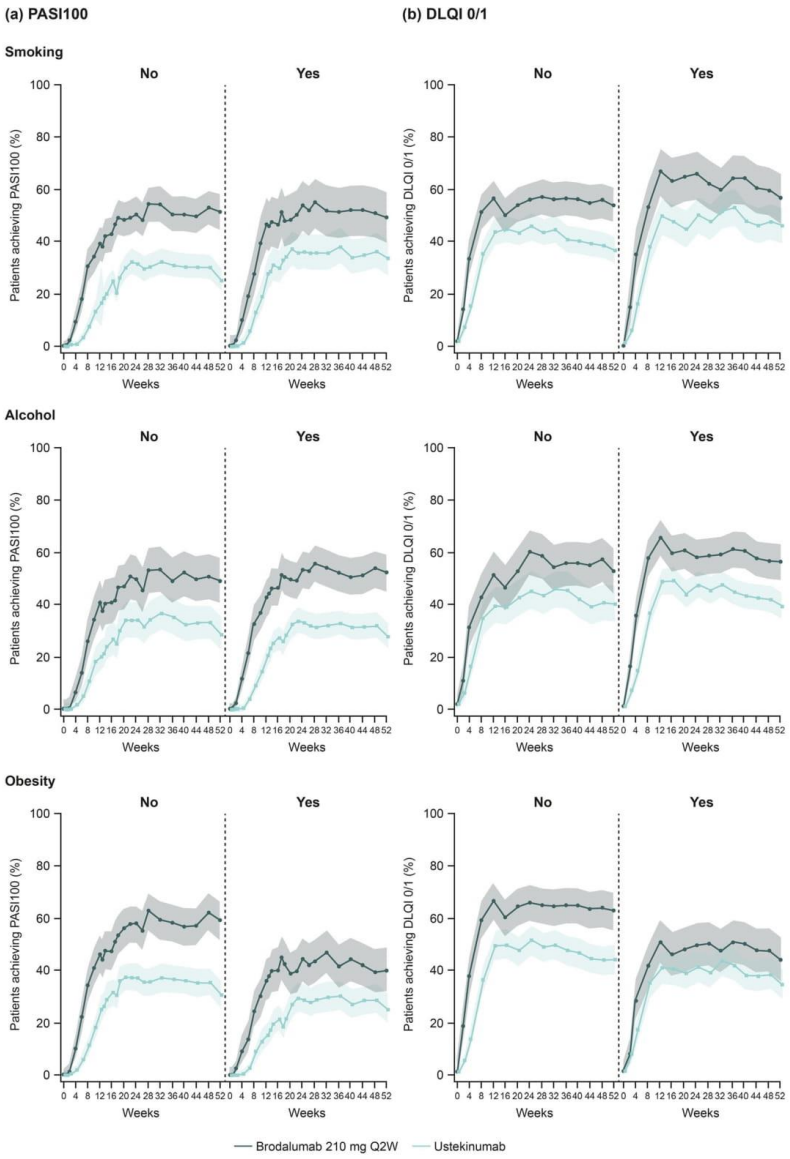


Fig. 5 Percentage of patients achieving **a** PASI100 and **b** DLQI 0/1 at weeks 4, 12, and 52 by history of lifestyle risk factors. Pooled data from the AMAGINE-2 and -3 trials. Shading indicates 95% confidence interval. *DLQI* Dermatology Life Quality Index, *PASI* Psoriasis Area and Severity Index, *Q2W* every 2 weeks

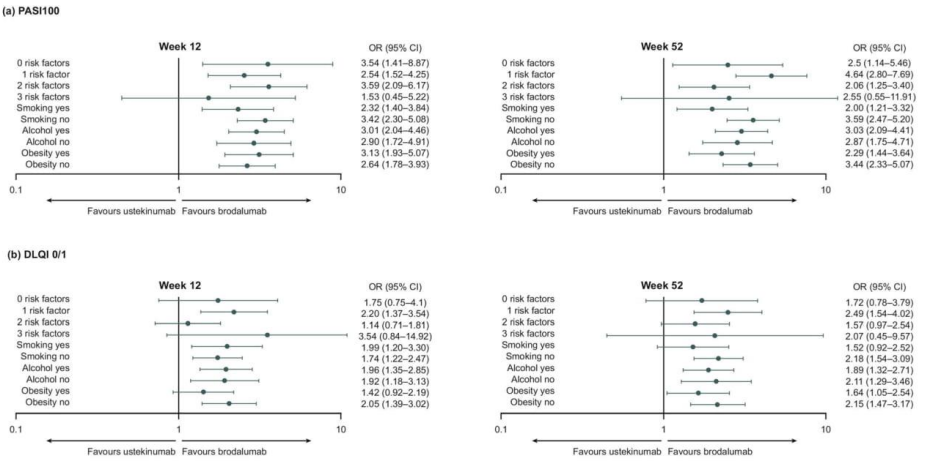


Fig. 6 Forest plots comparing the odds ratios and 95% confidence intervals for achieving **a** PASI100 and **b** DLQI 0/1 at weeks 12 and 52 by history of lifestyle risk factors. Pooled data from the AMAGINE-2 and -3 trials. *CI* confidence interval, *DLQI* Dermatology Life Quality Index, *OR* odds ratio, *PASI* Psoriasis Area and Severity Index

treated with anti-TNF-α therapies, smoking in combination with high BMI and a high baseline PASI score was a risk factor for lack of response [39]. Thus, there is a need for therapeutic strategies that remain effective in patients with aggravating and potentially treatment-confounding lifestyle factors.

In this analysis, which included 929 patients with moderate-to-severe psoriasis from the AMAGINE-2 and -3 studies, approximately 85% of patients had one or more risk factors (obesity or tobacco or alcohol use) at baseline.

We assessed the reduction in disease severity (PASI100 and PSI response) and impact on patient QoL, as estimated by the DLQI 0/1, through 52 weeks by obesity (< 30 versus ≥ 30 kg/m^2), and/or tobacco use (yes/no), and/or alcohol use (yes/no) per risk group (no risk factors, one risk factor, two risk factors, or three risk factors). We found that complete clearance (PASI100) was achieved more rapidly in more patients treated with brodalumab versus ustekinumab in the subgroups with no, one, or two baseline risk factors.

More patients achieved PSI response (total PSI ≤ 8) or DLQI 0/1 with brodalumab than with ustekinumab through to week 52, but these differences did not reach statistical significance. Thus, while Q12W administration of ustekinumab may be more convenient for patients, these data suggest a trend towards improvements in the severity of psoriasis signs and symptoms with brodalumab treatment.

Responder analysis for complete clearance or DLQI 0/1 by lifestyle risk factors showed a higher proportion of patients achieving PASI100 and DLQI through week 52 with brodalumab treatment in the alcohol use subgroup only. While a trend was observed in the smoking and obesity subgroups, statistical significance was not reached, most likely due to the smaller number of patents in these subgroups compared with the alcohol use subgroup (alcohol use was by far the most common risk factor at baseline).

These findings are similar to those of a previous analysis of AMAGINE-2 and -3 data showing that treatment with brodalumab resulted in rapid and higher proportions of

patients achieving complete skin clearance, rapid improvement in QoL, and a greater cumulative benefit for complete skin clearance versus ustekinumab and across subgroups with a history of alcohol and tobacco use [40]. It is possible that lifestyle factors may negatively impact the efficacy of any therapy for patients with psoriasis. However, they had no impact on the demonstrated benefits of brodalumab over ustekinumab in this analysis.

The body of evidence regarding the effects of lifestyle modifications, including weight-loss and smoking-cessation programs as well as trigger-factor elimination, in the management of psoriasis is limited. However, some studies suggest that lifestyle changes, such as a low-calorie diet, may supplement the pharmacologic treatment of obese psoriasis patients [41, 42]. More recently, a systematic review, which included ten randomized controlled trials with 1163 participants, found that dietary intervention may reduce psoriasis severity in obese patients and improve QoL compared with standard care [43].

There are several limitations to this study. The data analyzed were from a clinical trial population with strict entry criteria and may not be representative of real-world patient populations. Notably, AMAGINE-2 and -3 excluded patients who had prior ustekinumab experience, resulting in a high number of biologic-naïve patients, and this may have resulted in better response than would be observed in a real-world population [44]. Analyses were of pooled data from clinical trials that were not designed or statistically powered to assess these specific endpoints. Analyses were also restricted to patients in constant treatment arms, reducing the number of available patients that could be included. Finally, PASI is a subjective measure of disease severity. However, participating sites were encouraged to maintain the same rater for each patient to diminish between-rater bias.

CONCLUSIONS

The results of these analyses suggest that higher proportions of patients achieve complete skin clearance, PSI response, and QoL improvement with brodalumab compared with ustekinumab, regardless of history of risk factors, which are extremely common in real-world practice. Furthermore, these higher proportions of response are sustained over time. Thus, brodalumab may offer a good treatment option for psoriasis patients who have a history of aggravating lifestyle risk factors.

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Compliance with Ethics Guidelines. The study protocols for the AMAGINE-2 and AMAGINE-3 trials were approved by the institutional review boards at each participating centre. Both studies were conducted in accordance with the International Conference on Harmonisation guideline for Good Clinical Practice, the Declaration of Helsinki, and the Health Insurance Portability and Accountability Act of 1996 or relevant regional regulations. All subjects provided informed consent to participate in the study.

Data Availability. The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Prior Presentation. These data were previously presented at the 28th European Academy of Dermatology and Venereology (EADV) Congress, 9–13 October 2019, Madrid, Spain.

REFERENCES

1. Krueger G, Koo J, Lebwohl M, Menter A, Stern RS, Rolstad T. The impact of psoriasis on quality of life: results of a 1998 National Psoriasis Foundation patient-membership survey. Arch Dermatol. 2001;137(3):280–4.
2. Greb JE, Goldminz AM, Elder JT, Lebwohl MG, Gladman DD, Wu JJ, et al. Psoriasis. Nat Rev Dis Primers. 2016;2:16082.
3. Kamiya K, Kishimoto M, Sugai J, Komine M, Ohtsuki M. Risk factors for the development of psoriasis. Int J Mol Sci. 2019;20(18):4347.
4. Capon F (2017) The genetic basis of psoriasis. Int J Mol Sci. 18(12):2526
5. Parisi R, Webb RT, Carr MJ, Moriarty KJ, Kleyn CE, Griffiths CEM, et al. Alcohol-related mortality in patients with psoriasis: a population-based cohort study. JAMA Dermatol. 2017;153(12):1256–62.
6. Svanström C, Lonne-Rahm SB, Nordlind K. Psoriasis and alcohol. Psoriasis (Auckl). 2019;9:75–9.
7. Gupta MA, Schork NJ, Gupta AK, Ellis CN. Alcohol intake and treatment responsiveness of psoriasis: a prospective study. J Am Acad Dermatol. 1993;28(5 Pt 1):730–2.
8. Armstrong AW, Armstrong EJ, Fuller EN, Sockolov ME, Voyles SV. Smoking and pathogenesis of psoriasis: a review of oxidative, inflammatory and genetic mechanisms. Br J Dermatol. 2011;165(6):1162–8.
9. Armstrong AW, Harskamp CT, Dhillon JS, Armstrong EJ. Psoriasis and smoking: a systematic review and meta-analysis. Br J Dermatol. 2014;170(2):304–14.

10. Naldi L. Psoriasis and smoking: links and risks. Psoriasis (Auckl). 2016;6:65–71.

11. Richer V, Roubille C, Fleming P, Starnino T, McCourt C, McFarlane A, et al. Psoriasis and smoking: a systematic literature review and meta-analysis with qualitative analysis of effect of smoking on psoriasis severity. J Cutan Med Surg. 2016;20(3):221–7.

12. Thorneloe RJ, Bundy C, Griffiths CE, Ashcroft DM, Cordingley L. Adherence to medication in patients with psoriasis: a systematic literature review. Br J Dermatol. 2013;168(1):20–31.

13. Warren RB, Smith CH, Yiu ZZN, Ashcroft DM, Barker J, Burden AD, et al. Differential drug survival of biologic therapies for the treatment of psoriasis: a prospective observational cohort study from the British Association of Dermatologists Biologic Interventions Register (BADBIR). J Invest Dermatol. 2015;135(11):2632–40.

14. Paroutoglou K, Papadavid E, Christodoulatos GS, Dalamaga M. Deciphering the association between psoriasis and obesity: current evidence and treatment considerations. Curr Obes Rep. 2020;9(3):165–78.

15. World Health Organization. Body mass index-BMI. Available from: https://www.euro.who.int/en/health-topics/disease-prevention/nutrition/a-healthy-lifestyle/body-mass-index-bmi. Accessed Aug 2020.

16. Gordon KB, Blauvelt A, Foley P, Song M, Wasfi Y, Randazzo B, et al. Efficacy of guselkumab in subpopulations of patients with moderate-to-severe plaque psoriasis: a pooled analysis of the phase III VOYAGE 1 and VOYAGE 2 studies. Br J Dermatol. 2018;178(1):132–9.

17. Warren RB, Marsden A, Tomenson B, Mason KJ, Soliman MM, Burden AD, et al. Identifying demographic, social and clinical predictors of biologic therapy effectiveness in psoriasis: a multicentre longitudinal cohort study. Br J Dermatol. 2019;180(5):1069–76.

18. Jabbar-Lopez ZK, Yiu ZZN, Ward V, Exton LS, Mohd Mustapa MF, Samarasekera E, et al. Quantitative evaluation of biologic therapy options for psoriasis: a systematic review and network meta-analysis. J Invest Dermatol. 2017;137(8):1646–54.

19. Mrowietz U, Steinz K, Gerdes S. Psoriasis: to treat or to manage? Exp Dermatol. 2014;23(10):705–9.

20. Russell CB, Rand H, Bigler J, Kerkof K, Timour M, Bautista E, et al. Gene expression profiles normalized in psoriatic skin by treatment with brodalumab, a human anti-IL-17 receptor monoclonal antibody. J Immunol. 2014;192(8):3828–36.

21. Frieder J, Kivelevitch D, Menter A. Secukinumab: a review of the anti-IL-17A biologic for the treatment of psoriasis. Ther Adv Chronic Dis. 2018;9(1):5–21.

22. Syed YY. Ixekizumab: a review in moderate to severe plaque psoriasis. Am J Clin Dermatol. 2017;18(1):147–58.

23. Papp KA, Reich K, Paul C, Blauvelt A, Baran W, Bolduc C, et al. A prospective phase III, randomized, double-blind, placebo-controlled study of brodalumab in patients with moderate-to-severe plaque psoriasis. Br J Dermatol. 2016;175(2):273–86.

24. Lebwohl M, Strober B, Menter A, Gordon K, Weglowska J, Puig L, et al. Phase 3 studies comparing brodalumab with ustekinumab in psoriasis. N Engl J Med. 2015;373(14):1318–28.

25. Mrowietz U, Kragballe K, Reich K, Spuls P, Griffiths CE, Nast A, et al. Definition of treatment goals for moderate to severe psoriasis: a European consensus. Arch Dermatol Res. 2011;303(1):1–10.

26. Papp KA, Leonardi CL, Blauvelt A, Reich K, Korman NJ, Ohtsuki M, et al. Ixekizumab treatment for psoriasis: integrated efficacy analysis of three double-blinded, controlled studies (UNCOVER-1, UNCOVER-2, UNCOVER-3). Br J Dermatol. 2018;178(3):674–81.

27. Blauvelt A, Reich K, Tsai TF, Tyring S, Vanaclocha F, Kingo K, et al. Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate-to-severe plaque psoriasis up to 1 year: results from the CLEAR study. J Am Acad Dermatol. 2017;76(1):60-9.e9.

28. Blauvelt A, Papp KA, Griffiths CE, Randazzo B, Wasfi Y, Shen YK, et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the continuous treatment of patients with moderate to severe psoriasis: results from the phase III, double-blinded, placebo- and active comparator-controlled VOYAGE 1 trial. J Am Acad Dermatol. 2017;76(3):405–17.

29. Gordon KB, Strober B, Lebwohl M, Augustin M, Blauvelt A, Poulin Y, et al. Efficacy and safety of risankizumab in moderate-to-severe plaque psoriasis (UltIMMa-1 and UltIMMa-2): results from two double-blind, randomised, placebo-controlled and ustekinumab-controlled phase 3 trials. Lancet. 2018;392(10148):650–61.

30. Reich K, Armstrong AW, Foley P, Song M, Wasfi Y, Randazzo B, et al. Efficacy and safety of

guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the treatment of patients with moderate to severe psoriasis with randomized withdrawal and retreatment: Results from the phase III, double-blind, placebo- and active comparator-controlled VOYAGE 2 trial. J Am Acad Dermatol. 2017;76(3):418–31.

31. Strober B, Papp KA, Lebwohl M, Reich K, Paul C, Blauvelt A, et al. Clinical meaningfulness of complete skin clearance in psoriasis. J Am Acad Dermatol. 2016;75(1):77-82.e7.

32. Viswanathan HN, Mutebi A, Milmont CE, Gordon K, Wilson H, Zhang H, et al. Measurement properties of the psoriasis symptom inventory electronic daily diary in patients with moderate to severe plaque psoriasis. Value Health. 2017;20(8):1174–9.

33. Viswanathan HN, Chau D, Milmont CE, Yang W, Erondu N, Revicki DA, et al. Total skin clearance results in improvements in health-related quality of life and reduced symptom severity among patients with moderate to severe psoriasis. J Dermatolog Treat. 2015;26(3):235–9.

34. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)–a simple practical measure for routine clinical use. Clin Exp Dermatol. 1994;19(3):210–6.

35. Aalen OO, Johansen S. An empirical transition matrix for non-homogeneous Markov chains based on censored observations. Scand J Stat. 1978;5(3):141–50.

36. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc. 1999;94(446):496–509.

37. Gray RJ. A class of K-sample tests for comparing the cumulative incidence of a competing risk. Ann Stat. 1988;16(3):1141–54.

38. Mourad A, Straube S, Armijo-Olivo S, Gniadecki R. Factors predicting persistence of biologic drugs in psoriasis: a systematic review and meta-analysis. Br J Dermatol. 2019;181(3):450–8.

39. Di Lernia V, Ricci C, Lallas A, Ficarelli E. Clinical predictors of non-response to any tumor necrosis factor (TNF) blockers: a retrospective study. J Dermatolog Treat. 2014;25(1):73–4.

40. Kokolakis G SNV, Faurby MD, Carrascosa JM. Brodalumab versus ustekinumab: complete skin clearance and improvements in quality of life—A subgroup analysis according to lifestyle factors (tobacco and alcohol). EADV 2019. Poster P0438.

41. Gisondi P, Del Giglio M, Di Francesco V, Zamboni M, Girolomoni G. Weight loss improves the response of obese patients with moderate-to-severe chronic plaque psoriasis to low-dose cyclosporine therapy: a randomized, controlled, investigator-blinded clinical trial. Am J Clin Nutr. 2008;88(5):1242–7.

42. Gelfand JM, Abuabara K. Diet and weight loss as a treatment for psoriasis. Arch Dermatol. 2010;146(5):544–6.

43. Ko SH, Chi CC, Yeh ML, Wang SH, Tsai YS, Hsu MY. Lifestyle changes for treating psoriasis. Cochrane Database Syst Rev. 2019;7(7): Cd011972.

44. Karczewski J, Poniedziałek B, Rzymski P, Adamski Z. Factors affecting response to biologic treatment in psoriasis. Dermatol Ther. 2014;27(6):323–30.

Brodalumab is associated with high rates of complete clearance and quality of life improvement: A subgroup analysis of patients with psoriasis and concomitant psoriatic arthritis

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Kokolakis G, Vadstrup K, Hansen JB, Carrascosa JM

Die Psoriasisarthritis stellt ein chronisches entzündliches Krankheitsbild dar, welches mit der Psoriasis assoziiert ist und zu einer signifikanten körperlichen Funktionseinschränkung sowie zu einer verringerten Lebensqualität führen kann. Zur Vermeidung eines Fortschreitens der PsA mit Entwicklung von irreversiblen Gelenkdestruktionen ist eine adäquate Therapie bei Auftreten der Erkrankung notwendig. Das Ziel der vorliegenden Arbeit ist ein Vergleich der Therapie mit dem monoklonalen Antikörper gegen den Interleukin (IL)-17-Rezeptor A, Brodalumab, und dem monoklonalen Antikörper gegen die p40 Untereinheit von IL-12 und IL-23, Ustekinumab, im Hinblick auf die klinische Wirksamkeit und den Einfluss auf die Lebensqualität bei Patient:innen mit moderater bis schwerer Pso und vorliegender PsA. Es wurde eine post-hoc-Analyse der zusammengefassten Daten aus den Phase 3 Studien AMAGINE-2 und -3 durchgeführt. In den Studien erfolgte die Erfassung des kompletten Rückgangs der Hautveränderungen mittels Psoriasis Area and Severity Index (PASI; PASI100 – Rückgang der Hautveränderungen um 100%), der Verbesserung der Schwere der Symptome mittels Psoriasis Symptom Inventory (PSI – Ziel-Punktwert≤8), der Lebensqualität (Dermatology Life Quality Index (DLQI – Ziel-Punktwert: 0/1) sowie des Vorliegens einer begleitenden PsA. Mittels konkurrierendem Risikomodell erfolgte die Analyse der kumulativen Inzidenz eines PASI100 oder einem unzureichenden klinischen Ansprechen über den Studienzeitraum von 52 Wochen. Insgesamt wurden 929 Patient:innen mit moderater bis schwerer Pso zur Analyse eingeschlossen. Eine begleitende PsA war bei n=79/339 (23%) der Patient*innen unter Therapie mit Brodalumab und bei n=110/590 (19%) der Patient*innen unter Therapie mit Ustekinumab vorliegend. Nach 52 Wochen betrug das Chancenverhältnisse (95% Konfidenzintervall) für eine komplette Remission der Hautveränderungen (PASI100) unter Therapie mit Brodalumab im Vergleich zu einer Therapie mit Ustekinumab 3.15 (1.52–6.55, p=0.0015) in der Patient:innengruppe mit begleitender PsA und 3.05 (2.19–4.26, p<0.0001) in Patient:innengruppe ohne begleitende PsA. Unter Therapie mit Brodalumab im Vergleich zu einer Therapie mit Ustekinumab betrugen die Chancenverhältnisse (95% Konfidenzintervall) für einen DLQI-Wert von 0/1 2.05 (1.07–3.90, p=0.0277) und 1.83 (1.32–2.53, p=0.0002) sowie entsprechend für einen PSI≤8 3.42 (1.43–8.18, p = 0.0036) und 1.40 (1.01–1.95, p = 0.0434), jeweils für die Patient:innengruppe mit begleitender PsA und ohne begleitende PsA. Die kumulative Inzidenz der Patient:innen, welche einen PASI100 im Zeitraum der 52 Wochen erreicht hatten, war für die Brodalumab-

Gruppe sowohl für Patient:innen mit begleitender PsA (p=0.0001) als auch ohne begleitende PsA (p <0.0001) höher, verglichen mit der Ustekinumab-Gruppe. Zusammenfassend, führt die Therapie mit Brodalumab im Vergleich zu einer Therapie mit Ustekinumab bei Patient:innen mit moderater bis schwerer Psoriasis zu einer hohen Rate an komplettem klinischen Ansprechen und einem höheren kumulativen therapeutischen Vorteil. Diese Überlegenheit von Brodalumab gegenüber Ustekinumab ist unabhängig vom Vorliegen/Nichtvorliegen einer PsA. Um eine komplette Remission der Hautveränderungen und eine ausgesprochene Verbesserung der Lebensqualität bei Psoriasispatient:innen unabhängig vom gleichzeitigen Vorliegen einer PsA zu erreichen, ist die Blockade des IL-17 durch Brodalumab gegenüber der Blockade von IL12/IL-23 durch Ustekinumab zu bevorzugen.

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Brodalumab Is Associated with High Rates of Complete Clearance and Quality of Life Improvement: A Subgroup Analysis of Patients with Psoriasis and Concomitant Psoriatic Arthritis

Georgios Kokolakis[a] Kasper Vadstrup[b] Jes B. Hansen[b]
Jose Manuel Carrascosa[c]

[a]Psoriasis Research and Treatment Centre, Clinic of Dermatology, Venereology and Allergology, Charité – Universitätsmedizin Berlin, Berlin, Germany; [b]LEO Pharma A/S, Ballerup, Denmark; [c]Department of Dermatology, Hospital Universitari Germans Trias i Pujol, Universitat Autònoma of Barcelona, IGTP, Badalona, Spain

Keywords
Brodalumab · Ustekinumab · Psoriasis · Psoriatic arthritis · QoL

Abstract
Background: Psoriatic arthritis (PsA) is a chronic inflammatory disease associated with psoriasis that significantly impairs physical function and quality of life (QoL). Prompt therapeutic intervention is crucial for limiting PsA progression and preventing disability. ***Objectives:*** The aim of this study was to compare the efficacy of brodalumab versus ustekinumab and the impact on QoL in patients with moderate-to-severe plaque psoriasis, by concomitant PsA status. ***Methods:*** This post hoc analysis of pooled data from the phase 3 AMAGINE-2 and -3 trials evaluated complete skin clearance (100% improvement of Psoriasis Area and Severity Index [PASI 100]), improvement in symptom severity (Psoriasis Symptom Inventory [PSI] response), and QoL (Dermatology Life Quality Index [DLQI] score of 0/1) by concomitant PsA status. A competing risk model assessed cumulative incidence over 52 weeks with outcomes of PASI 100 or inadequate response. ***Results:*** This analysis included 929 patients with moderate-to-severe psoriasis. Concomitant PsA was present in 79/339 (23%) and 110/590 (19%) patients receiving brodalumab 210 mg and ustekinumab, respectively. At Week 52, odds ratios (ORs) (95% confidence intervals [CIs]) for complete clearance with brodalumab versus ustekinumab were 3.15 (1.52–6.55, $p = 0.0015$) in patients with concomitant PsA and 3.05 (2.19–4.26, $p < 0.0001$) in patients without concomitant PsA. Corresponding Week 52 ORs (95% CIs) for DLQI 0/1 with brodalumab versus ustekinumab were 2.05 (1.07–3.90, $p = 0.0277$) and 1.83 (1.32–2.53, $p = 0.0002$); Week 52 ORs (95% CIs) for PSI ≤8 with brodalumab versus ustekinumab were 3.42 (1.43–8.18, $p = 0.0036$) and 1.40 (1.01–1.95, $p = 0.0434$). The 52-week cumulative incidence of patients achieving PASI 100 was significantly higher for brodalumab versus ustekinumab in patients with concomitant PsA ($p = 0.0001$) and in those without concomitant PsA ($p < 0.0001$). ***Conclusions:*** Treatment with brodalumab rapidly results in high levels of complete and sustained skin clearance and greater cumulative treatment benefit in patients with moderate-to-severe psoriasis versus ustekinumab, regardless of concomitant PsA status.

karger@karger.com
www.karger.com/drm

Correspondence to:
Georgios Kokolakis, georgios.kokolakis@charite.de

Introduction

Psoriatic arthritis (PsA) is a chronic inflammatory musculoskeletal disorder estimated to affect up to 40% of patients with psoriasis [1]. PsA affects both the joints and the entheses and can lead to progressive joint destruction, disability and significantly impaired quality of life (QoL) [2, 3]. Like psoriasis, PsA is also associated with an increased risk of comorbidities, such as obesity, insulin resistance, inflammatory bowel disease and cardiovascular disease [4–6].

The early diagnosis and treatment of PsA are crucial to reduce the risk of joint damage, disability and comorbidities [7–9]. Since PsA usually occurs after the development of psoriasis [10], it is important that patients with psoriasis are routinely screened for signs of PsA. The therapeutic goals for patients with PsA are to minimise disease activity, prevent disease progression, alleviate symptoms, improve QoL and restore functional ability [10, 11]. Treatment decisions are based on disease severity, joint involvement and associated skin symptoms [12].

There have been significant advances in our understanding of the pathogenesis of PsA in recent years, which have led to advances in the treatment of the disease, including the introduction of biologics targeting tumour necrosis factor alpha (TNF-α), interleukin (IL)-12/23, IL-17A and IL-23 [13]. Randomised controlled trials have established the efficacy of the anti-IL-12/23 monoclonal antibody ustekinumab in the treatment of patients with active PsA who had previously received conventional and/or anti-TNF biological agents [14, 15]. More recently, guselkumab, a monoclonal antibody that selectively inhibits IL-23, was approved for the treatment of patients with active PsA [16–18]. However, a significant proportion of patients with PsA fail to have a sustained response to biologics [6, 19], and head-to-head studies of biologics in patients with PsA are needed to better inform treatment choices [3].

Brodalumab is a fully human monoclonal antibody with a unique mechanism of action. It binds with high affinity to the IL-17 receptor subunit A (IL-17 RA), thereby inhibiting downstream signalling of multiple IL-17 family cytokines (IL-17A, IL-17F, IL-17C, IL-17E) involved in the pathogenesis of psoriasis [20], unlike other anti-IL-17 biologics, such as secukinumab and ixekizumab, which specifically target IL-17A [21, 22]. Brodalumab is currently approved for the treatment of moderate-to-severe plaque psoriasis [23, 24] in the USA, EU, Canada and some Asian countries, and for PsA in Japan [25].

Brodalumab demonstrated high rates of total skin clearance, as shown by 100% reduction in Psoriasis Area and Severity Index (PASI 100), in two phase 3 trials in patients with moderate-to-severe plaque psoriasis: AMAGINE-2 and AMAGINE-3 [26]. Brodalumab has also demonstrated efficacy relative to placebo in phase 2 and 3 trials in patients with PsA [6, 27]. The aim of this post hoc analysis was to evaluate the efficacy of brodalumab compared to ustekinumab and the impact on patient QoL through 52 weeks in patients with moderate-to-severe plaque psoriasis, with or without concomitant PsA, using pooled data from the phase 3 AMAGINE-2 and AMAGINE-3 trials.

Materials and Methods

Study Design and Patients

The AMAGINE-2 (NCT01708603) and AMAGINE-3 (NCT01708629) trial designs have been previously reported in detail [26] and are illustrated in online supplementary Figure S1 (see www.karger.com/doi/10.1159/000520290 for all online suppl. material). Briefly, patients ≥18 years of age with moderate-to-severe plaque psoriasis (defined as a PASI score ≥12, static Physician's Global Assessment [sPGA] score of ≥3 and ≥10% body surface area involvement of ≥6 months' duration) were randomised 2:2:1:1 to receive brodalumab 210 mg, brodalumab 140 mg, ustekinumab (45 mg for patients with a body weight ≤100 kg and 90 mg for patients >100 kg on Day 1, Week 4 and every 12 weeks [Q12W] thereafter) or placebo on Day 1 and Weeks 1, 2, 4, 6, 8 and 10. At Week 12, patients who were originally randomised to brodalumab were re-randomised 2:2:2:1 to receive a brodalumab maintenance regimen of 210 mg once every 2 weeks (Q2W) or 140 mg Q2W, every 4 weeks (Q4W) or every 8 weeks (Q8W). Placebo patients received 210 mg of brodalumab Q2W, and ustekinumab patients continued to receive ustekinumab Q12W until Week 52.

Patients who had an inadequate response (defined as sPGA ≥3 or persistent values of 2 over a ≥4-week period at, or after, Week 16) received rescue treatment with brodalumab 210 mg. After Week 16 and through Week 52, patients receiving brodalumab were rescued with brodalumab 210 mg Q2W, while those receiving ustekinumab remained on ustekinumab except at Week 16, when they could receive rescue treatment (210 mg of brodalumab Q2W). Rescue treatment was blinded. Patients who did not respond to rescue treatment for ≥12 weeks had treatment discontinued.

The AMAGINE-2 and AMAGINE-3 trials were conducted in accordance with the International Conference on Harmonisation for Good Clinical Practice, the Declaration of Helsinki, and the Health Insurance Portability and Accountability Act of 1996 or relevant regional regulations. The institutional review boards at each participating centre approved the study protocols.

Assessments

Concomitant PsA Status

Concomitant PsA status was defined by medical history and categorised in yes/no options.

Table 1. Baseline demographic and disease characteristics (pooled data by treatment arm and concomitant PsA status from the AMAGINE-2 and -3 trials)

	Brodalumab (*n* = 339)		Ustekinumab (*n* = 590)	
	PsA yes (*n* = 79) (23.3%)	PsA no (*n* = 260) (76.7%)	PsA yes (*n* = 110) (18.6%)	PsA no (*n* = 480) (81.4%)
Female, *n* (%)	32.0 (40.5)	77.0 (29.6)	42.0 (38.2)	144.0 (30.0)
Age, mean (SD), years	49.8 (13.5)	43.0 (13.0)	48.3 (11.7)	44.4 (13.3)
Weight, mean (SD), kg	92.8 (26.3)	89.6 (23.5)	91.2 (24.4)	91.0 (22.5)
Duration of disease, mean (SD), years	21.5 (11.5)	16.0 (11.5)	21.0 (12.2)	18.1 (12.2)
Prior biologic experience, *n* (%)	45.0 (57.0)	51.0 (19.6)	49.0 (44.5)	106.0 (22.1)
Prior biologic failure, *n* (%)	18.0 (40.0)	28.0 (54.9)	19.0 (38.8)	41.0 (38.7)
Prior systemic use, *n* (%)	61.0 (77.2)	133.0 (51.2)	78.0 (70.9)	262.0 (54.6)
CRP, mean (SD), mg/L	11.9 (17.2)	5.3 (9.9)	9.7 (20.1)	4.5 (5.5)
PASI, mean (SD)	21.3 (8.0)	20.2 (7.8)	21.4 (9.0)	19.7 (8.2)
DLQI, mean (SD)	15.9 (7.3)	14.4 (7.2)	14.6 (7.2)	14.9 (7.3)

CRP, C-reactive protein; DLQI, Dermatology Life Quality Index; PASI, Psoriasis Area and Severity Index; PsA, psoriatic arthritis; SD, standard deviation.

Disease Severity, Response and QoL

Disease severity was evaluated using the PASI and the Psoriasis Symptom Inventory (PSI). The PASI is the most widely used outcome measure for assessing disease severity in clinical trials of biologics to treat psoriasis [28]. The PSI is an 8-point, patient-reported outcome measure, which was developed by Amgen, for assessing the severity of psoriasis symptoms (i.e., itch, redness, scaling, burning, stinging, cracking, flaking and pain), with each symptom rated as either 0 (not at all severe), 1 (mild), 2 (moderate), 3 (severe) or 4 (very severe) [29]. PSI was assessed daily from screening through Week 24 and Weeks 48–52 and aggregated to a weekly score for patients with at least 4 values within that week. A PSI responder was defined as having a total score ≤8 and no item >1 throughout the week using 24-hour recall.

QoL was evaluated using the Dermatology Life Quality Index (DLQI). The DLQI consists of 10 questions covering 6 domains: symptoms and feelings, daily activities, leisure, work and school, personal relationships and bother with treatment. A score of 0 or 1 indicates no effect at all on a patient's life [30]. DLQI was assessed at Weeks 0, 2, 4 and every fourth week thereafter.

Responder Analyses for Clearance (PASI 100), PSI Responder Status and DLQI 0/1 at a Given Time Point (Weeks 0–52) by Concomitant PsA Status

Data from patients randomised to receive constant dosing of either the approved dose of brodalumab (210 mg Q2W) or ustekinumab for the entire 52-week treatment period, subdivided according to concomitant PsA status at baseline, were included in this analysis. The proportions of patients achieving PASI 100, PSI responder status and DLQI 0/1 response were compared according to concomitant PsA status and visit. Comparisons between treatment groups were reported as odds ratios (ORs) and 95% confidence intervals (CIs) calculated using the Cochran-Mantel-Haenszel method and adjusted for study, baseline total body weight group (≤100 kg, >100 kg), geographical region, and within study and subgroup baseline score (≤ median, > median).

Cumulative Benefit through 52 Weeks by Concomitant PsA Status

Cumulative benefit for each endpoint was determined as the area under the curve (AUC) over 52 weeks for PASI and change in DLQI and 24 weeks for PSI responder status by concomitant PsA status. The AUC was calculated using the trapezoidal rule:

$$\text{Total AUC} = \sum_{i}^{N} = {}_{0}\,\frac{1}{2}\left(P_i + P_{i+1}\right)\left(T_{i+1} + T_i\right),$$

where N = number of assessment time points, 0 = baseline, P_i = percentage of responders, T_i = time point.

Cumulative benefit was normalised to a percentage of the maximum possible nominal AUC of 5,200 for PASI 100 and DLQI 0/1 (based on a 100% response rate over 52 weeks) and 2,400 for PSI responder status (based on a 100% response rate over the first 24 weeks). A *t* test was used to test *p* values for treatment differences of brodalumab versus ustekinumab. AUC ratios (brodalumab total AUC value divided by ustekinumab total AUC value) were calculated, with values >1.0 indicating a greater clinical benefit for brodalumab versus ustekinumab, and 95% CIs were calculated via bootstrapping.

Cumulative Incidence of Complete Clearance over 52 Weeks by Concomitant PsA Status

Cumulative incidence of complete clearance over 52 weeks was analysed by concomitant PsA status using a Competing Risk model [31] with the outcome of (a) achieving PASI 100 or (b) inadequate response (defined as sPGA ≥3 or sPGA ≥2 for more than 4 weeks) at, or after, Week 16. Comparisons between treatment arms were performed using subdistribution hazard ratios (HRs) and associated χ^2 tests [32, 33] and adjusted for baseline characteristics, as detailed for the responder analyses. Non-responder imputation was used to handle missing data.

Results

Baseline Demographic and Disease Characteristics

A total of 929 patients (brodalumab 210 mg, $n = 339$; ustekinumab, $n = 590$) were included in this analysis. Concomitant PsA was present in 23% and 19% of patients receiving brodalumab and ustekinumab, respectively. Baseline demographic and disease characteristics were generally balanced across treatments (Table 1). For both the brodalumab and ustekinumab treatment groups, patients with concomitant PsA had longer disease duration, higher levels of C-reactive protein, and were more likely to have prior biologic experience compared with patients without PsA (Table 1).

Efficacy

Responder Analysis for Complete Clearance (PASI 100), PSI and DLQI 0/1 by Concomitant PsA Status

Treatment with brodalumab resulted in significantly more patients achieving complete clearance (PASI 100) compared with ustekinumab, from Week 4 through Week 52 for patients without PsA ($p < 0.001$) and from Week 6 through Week 52 for patients with PsA ($p < 0.05$) (Fig. 1a). ORs (95% CIs) for complete clearance with brodalumab versus ustekinumab at Week 52 were: with concomitant PsA, OR 3.15 (1.52–6.55, $p = 0.0015$); without concomitant PsA, OR 3.05 (2.19–4.26, $p < 0.0001$).

Treatment with brodalumab also resulted in significantly more patients achieving DLQI 0/1 compared with ustekinumab, from Week 2 through Week 52 for patients without PsA ($p < 0.05$). In patients with PsA, more patients achieved DLQI 0/1 compared with ustekinumab from Week 4 through Week 52, although significance was not reached at Weeks 16, 20, 24 and 32 due to lower numbers of patients in the compared brodalumab and ustekinumab groups (Fig. 1b). ORs (95% CIs) for DLQI 0/1 with brodalumab versus ustekinumab at Week 52 were: with concomitant PsA, OR 2.05 (1.07–3.90, $p = 0.0277$); without concomitant PsA, OR 1.83 (1.32–2.53, $p = 0.0002$).

Treatment with brodalumab also resulted in more patients achieving PSI responder status compared with ustekinumab from Week 2 through Week 52 in both groups, although significance was not reached at Weeks 14, 17, 19, 21 and 49 in the group with PsA and at Week 49 in the group without PsA due to lower numbers of patients in the compared brodalumab and ustekinumab groups (Fig. 1c). ORs (95% CIs) for PSI responder status with brodalumab versus ustekinumab at Week 52 were: with concomitant PsA, OR 3.42 (1.43–8.18, $p = 0.0036$); without concomitant PsA, OR 1.40 (1.01–1.95, $p = 0.0434$).

Cumulative Benefit through 52 Weeks by Concomitant PsA Status

Brodalumab treatment resulted in significantly greater cumulative benefit (PASI 100) compared with ustekinumab in the subgroups with and without concomitant PsA (Fig. 2a). AUC ratios were 1.84 ($p = 0.0001$) and 1.68 ($p < 0.0001$), respectively, in the subgroups with and without concomitant PsA.

Significant differences in cumulative treatment benefit favouring brodalumab versus ustekinumab were also observed for DLQI 0/1 (Fig. 2b). AUC ratios were 1.40 ($p = 0.0016$) and 1.33 ($p < 0.0001$), respectively, in the subgroups with and without concomitant PsA.

Similar findings were observed with respect to achievement of PSI responder status up to Week 24 (Fig. 2c). AUC ratios were 1.49 ($p = 0.0005$) and 1.34 ($p < 0.0001$), respectively, in the subgroups with and without concomitant PsA.

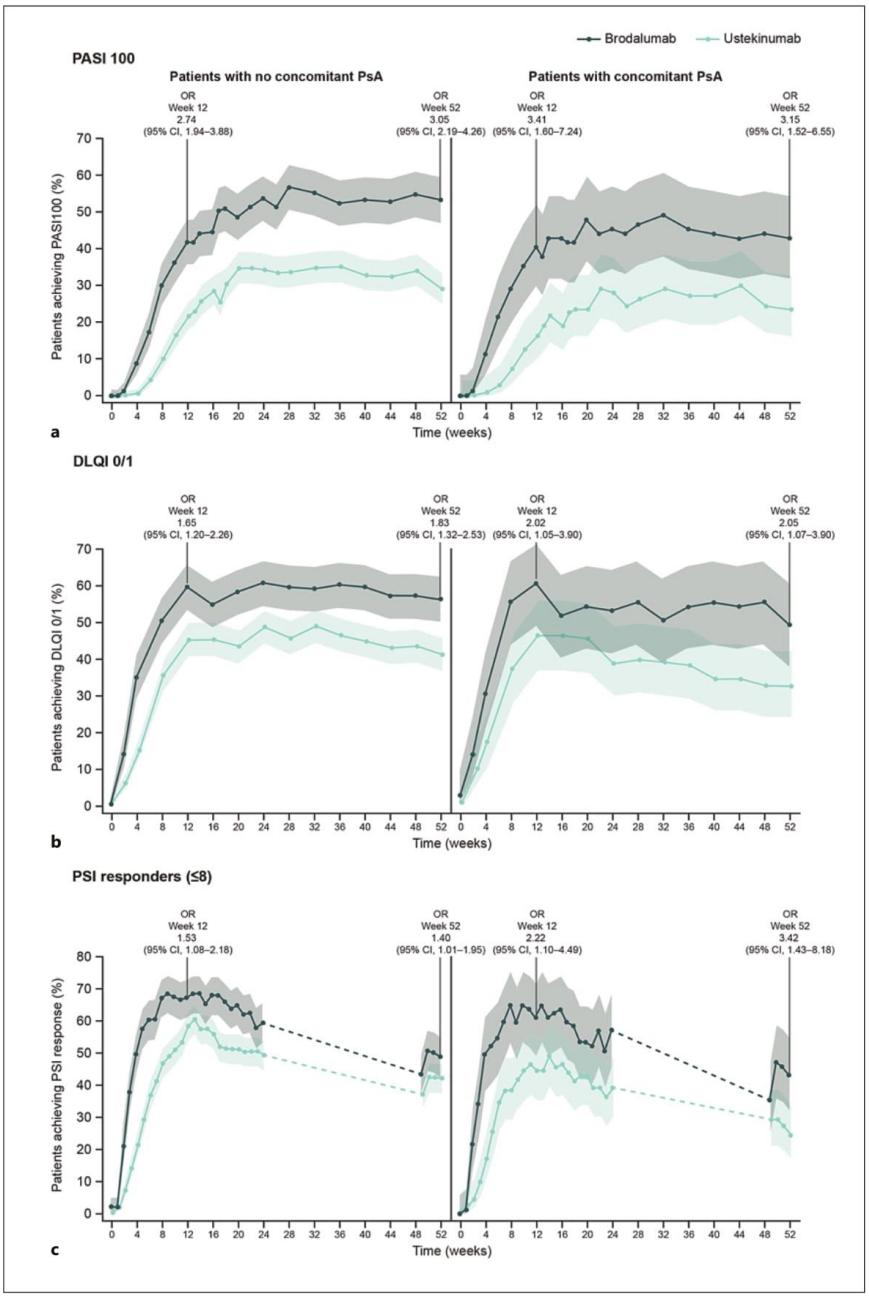
Competing Risk Model for Achieving Skin Clearance

The competing risk analysis of either achieving PASI 100 or having an inadequate response over 52 weeks showed that brodalumab patients with concomitant PsA were significantly more likely to achieve PASI 100 at least once over 52 weeks than ustekinumab patients, with 70.1% (95% CI, 60.4–81.5%) of responders on brodalumab versus 43.9% (95% CI, 35.4–54.3%) of responders on ustekinumab (HR 2.34; 95% CI, 1.61–3.38; $p < 0.0001$) (Fig. 3b). In patients without concomitant PsA, 76.1% (95% CI, 71.0–81.5%) of brodalumab patients achieved PASI 100 versus 53.2% (95% CI, 48.9–57.9%) of ustekinumab patients (HR 2.07; 95% CI, 1.71–2.50; $p < 0.0001$) (Fig. 3a). Furthermore, there were fewer inadequate responders to brodalumab compared with ustekinumab (Fig. 3a,b).

The median time to complete clearance was 13 weeks for brodalumab versus 36 weeks for ustekinumab in patients without PsA (Fig. 3a). In patients with concomitant PsA, the median time to complete clearance was 15 weeks for brodalumab but was indeterminable for ustekinumab, as less than 50% of patients achieved complete clearance by Week 52 (Fig. 3b).

Discussion/Conclusion

Previous studies have demonstrated the efficacy of brodalumab in patients with PsA [6, 27]. Brodalumab (140 mg or 280 mg Q2W) significantly improved clinical response rates versus placebo in patients with PsA in a



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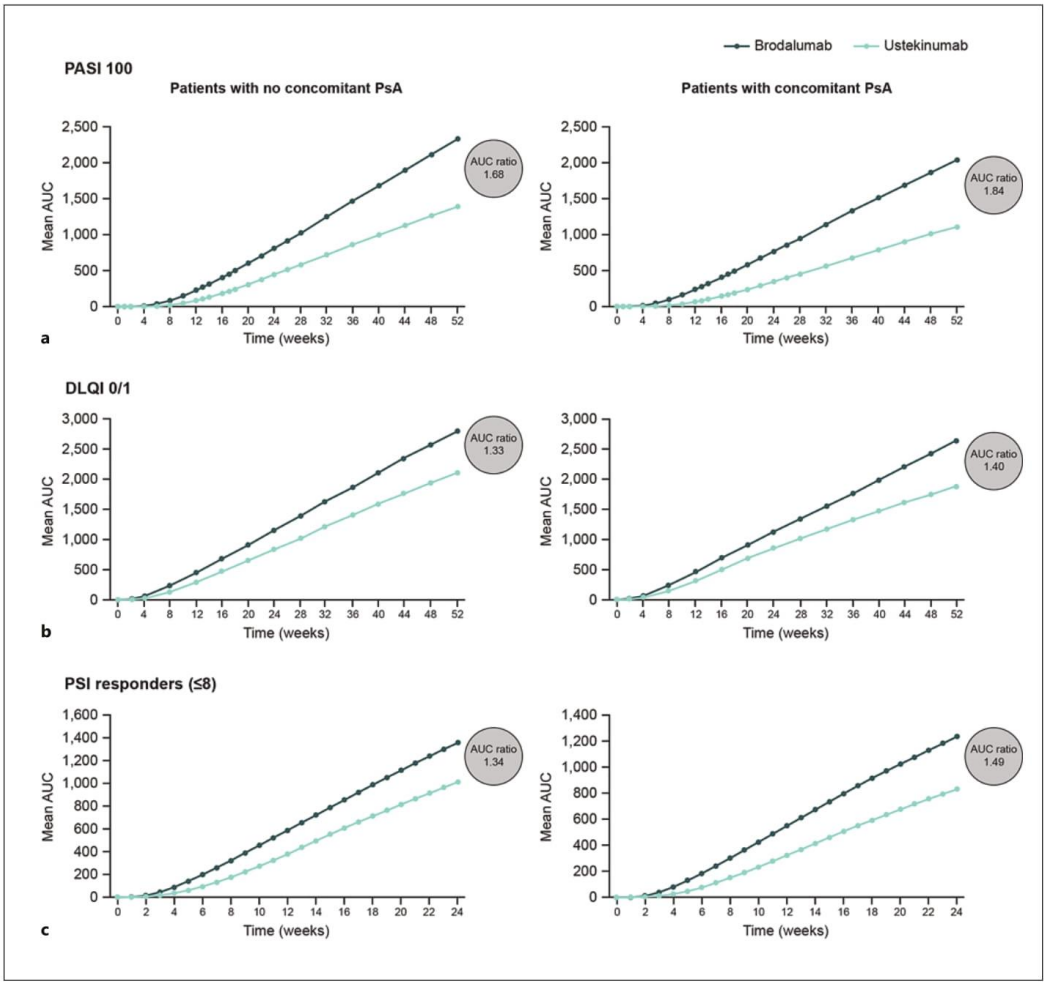

Fig. 2. Cumulative benefit through 52 weeks with respect to PASI 100 (**a**), DLQI 0/1 (**b**) and PSI responder (≤8) status (**c**), by visit, treatment and concomitant PsA status (NRI). AUC, area under the curve; DLQI, Dermatology Life Quality Index; NRI, non-responder imputation; PASI, Psoriasis Area and Severity Index; PsA, psoriatic arthritis; PSI, Psoriasis Symptom Inventory.

Fig. 1. Percentage of patients achieving PASI 100 (**a**), DLQI 0/1 (**b**) and PSI responder (≤8) status (**c**), by visit, treatment and concomitant PsA status (NRI).[a] Shading indicates 95% CI. PSI data were not collected between Weeks 24 and 48; indicated by a broken line. [a]This analysis included 929 patients who received brodalumab 210 mg (n = 339) or ustekinumab (n = 590). Of the patients who received brodalumab, 79 had concomitant PsA and 260 had no concomitant PsA; of those who received ustekinumab, 110 had concomitant PsA and 480 had no concomitant PsA. CI, confidence interval; DLQI, Dermatology Life Quality Index; NRI, non-responder imputation; OR, odds ratio; PASI, Psoriasis Area and Severity Index; PsA, psoriatic arthritis; PSI, Psoriasis Symptom Inventory.

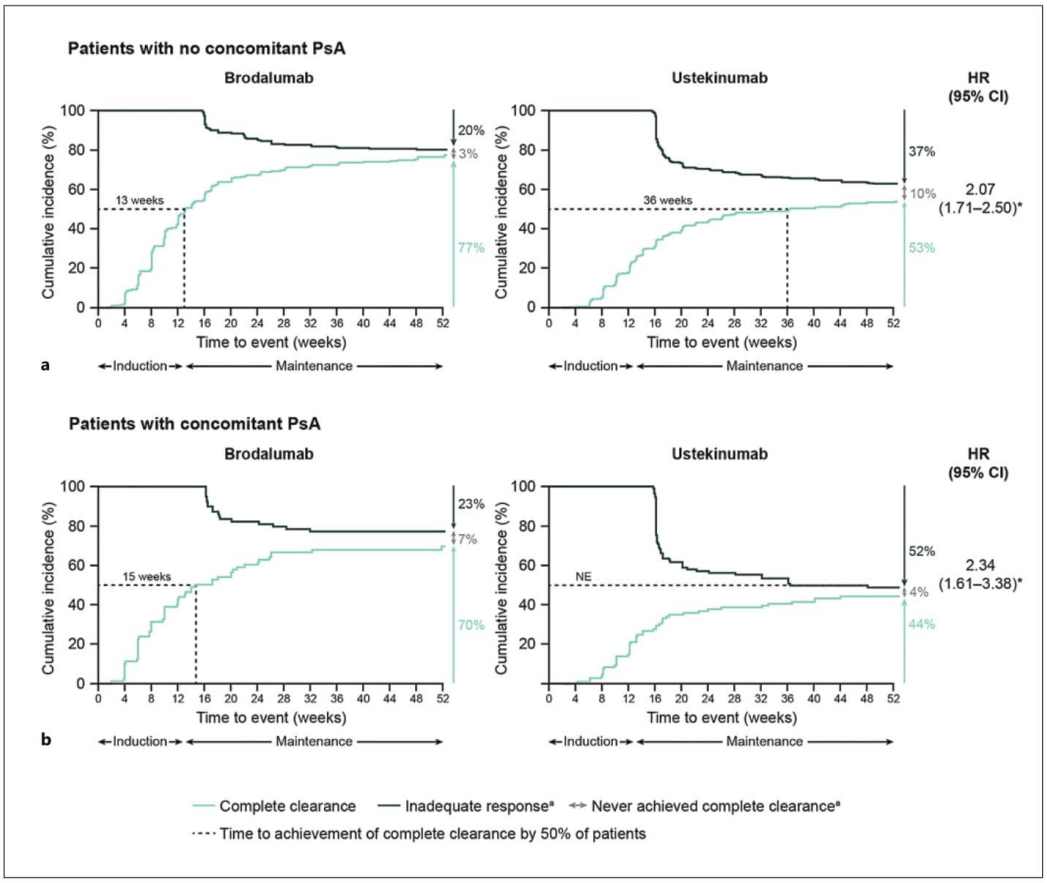

Fig. 3. Cumulative incidence of patients achieving PASI 100, by visit, treatment and concomitant PsA status (competing risk analysis) (NRI). *$p < 0.0001$. [a]Defined as static Physician's Global Assessment ≥3 or persistent values of 2 over at least a 4-week period or after Week 16. CI, confidence interval; HR, hazard ratio; NE, not estimable; NRI, non-responder imputation; PsA, psoriatic arthritis.

phase 2, randomised, double-blind, placebo-controlled trial [6]. The efficacy and safety of brodalumab in adults with active PsA and inadequate response, or intolerance, to conventional treatment were further evaluated in the phase 3 AMVISION-1 and AMVISION-2 trials. Brodalumab (140 mg or 210 mg once Q2W) was associated with rapid and significant improvements in signs and symptoms of PsA versus placebo [27].

In addition to musculoskeletal symptoms, cutaneous manifestations and severity of psoriasis are also important considerations when making treatment decisions for patients with PsA [12, 34]. In this pooled analysis of data from the phase 3 AMAGINE-2 and AMAGINE-3 trials, we assessed the reduction in disease severity and impact on patient QoL through 52 weeks, in patients with moderate-to-severe psoriasis, by presence or not of concomitant PsA. We found that brodalumab (210 mg once Q2W)

rapidly achieved higher levels of complete skin clearance (PASI 100), was significantly better at improving QoL and reducing patient-reported symptoms of psoriasis, and resulted in a greater cumulative treatment benefit through 52 weeks in patients with moderate-to-severe psoriasis than ustekinumab, regardless of concomitant PsA status.

In an earlier analysis of data from AMAGINE-2 and AMAGINE-3, brodalumab showed significantly higher PASI 75, 90 and 100 response rates versus ustekinumab [26]. In our analysis, a significantly higher proportion of brodalumab-treated than ustekinumab-treated patients achieved rapid and consistent complete skin clearance over the 52-week treatment period, with significant differences observed from Week 4 onwards for patients without PsA and from Week 6 onwards for patients with concomitant PsA. In addition to comparing the response to brodalumab versus ustekinumab at specific time points, we examined the cumulative treatment benefit and cumulative incidence of response to each drug over 52 weeks of treatment. Cumulative measures of drug efficacy – which account for speed, durability and magnitude of treatment responses – have been suggested to be particularly relevant for psoriasis and other chronic diseases that have continuous impact on patients [35]. These analyses demonstrated that brodalumab was associated with a greater cumulative benefit and a higher likelihood of achieving PASI 100 at least once over 52 weeks compared to ustekinumab, and that the differences were more prominent among patients with concomitant PsA than those without. Indeed, while 50% of brodalumab-treated patients with PsA had achieved PASI 100 at least once by week 15, there was no time through Week 52 at which 50% of ustekinumab-treated patients with PsA achieved PASI 100.

Achievement of PASI 100 was associated with improvement in QoL, as measured by DLQI 0/1, in patients with or without concomitant PsA. These findings reflect those of Warren et al. [36] who recently reported that improvement in QoL, as measured by DLQI 0/1, was associated with achievement of PASI 100 in patients receiving brodalumab. Furthermore, the improvement in QoL observed in our study was associated with a rapid reduction in the severity of psoriasis symptoms, as measured by PSI response. The likelihood of achieving PSI responder status favoured brodalumab in patients with or without concomitant PsA, although ORs were noticeably higher in the group with PsA, at both Weeks 12 and 52.

These data add to the growing body of evidence from clinical-trial and real-world settings suggesting that complete skin clearance is associated with substantially reduced physical burden of psoriasis, increased treatment satisfaction and improved QoL [37–42] and that rapid resolution of psoriasis symptoms correlates with improvements in QoL [43, 44].

Patients with PsA are considered high-need because of progressive joint symptoms/pain and disability [45]. Early diagnosis of PsA enables prompt treatment initiation, resulting in improved clinical outcomes and reduced disease severity and joint damage [45, 46]. Delays in diagnosis increase the risk of joint damage and poor long-term physical function [47]. As patients with psoriasis and without current PsA might go on to develop PsA [48] and because brodalumab is effective at treating psoriasis in patients with or without symptoms of PsA, early treatment of psoriasis with brodalumab might potentially prevent the evolution of PsA in asymptomatic patients.

This study had some limitations. Firstly, analyses were of pooled data from clinical trials not designed and statistically powered to assess these specific endpoints. Secondly, the data were from a clinical trial population with strict inclusion and exclusion criteria and may therefore not be representative of real-world patient populations. Additionally, concomitant PsA was defined by medical history, and details related to PsA clinical characteristics and treatment were not collected. Notably, it is likely that only patients with well-controlled PsA entered the AMAGINE-2 and AMAGINE-3 studies, resulting in a limited number of patients with psoriasis with concomitant PsA being included. Finally, analyses were restricted to patients in constant treatment arms, further reducing the number of patients included.

In conclusion, the results from this analysis of pooled data from the phase 3 AMAGINE-2 and AMAGINE-3 trials demonstrate that treatment with brodalumab rapidly results in high levels of complete and sustained skin clearance and greater cumulative treatment benefit in patients with moderate-to-severe psoriasis than treatment with ustekinumab, regardless of concomitant PsA status. Thus, brodalumab may offer an additional treatment strategy for patients with psoriasis with concomitant PsA.

Key Message

Brodalumab achieved PASI 100 and improved QoL in patients with psoriasis with and without concomitant PsA.

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Statement of Ethics

The AMAGINE-2 and AMAGINE-3 trials were conducted in accordance with the International Conference on Harmonisation for Good Clinical Practice, the Declaration of Helsinki, and the Health Insurance Portability and Accountability Act of 1996 or relevant regional regulations. The institutional review boards at each participating centre approved the study protocols. All patients provided written informed consent before the initiation of study procedures.

Conflict of Interest Statement

G.K. has received honoraria for participation in advisory boards, in clinical trials and/or as speaker from AbbVie Deutschland GmbH & Co. KG, Abbott GmbH, Actelion Pharmaceuticals Ltd., AMGEN GmbH, Basilea Pharmaceutica Ltd., Bayer AG, Biogen IDEC GmbH, Celgene GmbH, Hexal-Sandoz GmbH, Janssen-Cilag GmbH, LEO Pharma GmbH, Lilly Deutschland GmbH, MSD Sharp & Dohme GmbH, Novartis Pharma GmbH, Parexel International GmbH, Pfizer Deutschland GmbH and UCB Pharma GmbH. J.B.H. and K.V. are employees of LEO Pharma. J.M.C. has received honoraria for participation in advisory boards, in clinical trials and/or as speaker from AbbVie, AMGEN, Biogen, Celgene, Janssen-Cilag, LEO Pharma, Lilly, Novartis Pharma GmbH, Pfizer, UCB, Sandoz, Mylan and Almirall.

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Author Contributions

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Data Availability Statement

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request for non-commercial purposes.

References

1 Gladman DD, Antoni C, Mease P, Clegg DO, Nash P. Psoriatic arthritis: epidemiology, clinical features, course, and outcome. Ann Rheum Dis. 2005;64(Suppl 2):ii14–7.
2 Griffiths CEM, Jo SJ, Naldi L, Romiti R, Guevara-Sangines E, Howe T, et al. A multidimensional assessment of the burden of psoriasis: results from a multinational dermatologist and patient survey. Br J Dermatol. 2018;179(1):173–81.
3 Mahmood F, Coates LC, Helliwell PS. Current concepts and unmet needs in psoriatic arthritis. Clin Rheumatol. 2018;37(2):297–305.
4 Ferguson LD, Siebert S, McInnes IB, Sattar N. Cardiometabolic comorbidities in RA and PsA: lessons learned and future directions. Nat Rev Rheumatol. 2019;15(8):461–74.
5 Gudu T, Gossec L. Quality of life in psoriatic arthritis. Expert Rev Clin Immunol. 2018;14(5):405–17.
6 Mease PJ, Genovese MC, Greenwald MW, Ritchlin CT, Beaulieu AD, Deodhar A, et al. Brodalumab, an anti-IL17RA monoclonal antibody, in psoriatic arthritis. N Engl J Med. 2014;370(24):2295–306.
7 McArdle A, Pennington S, FitzGerald O. Clinical features of psoriatic arthritis: a comprehensive review of unmet clinical needs. Clinic Rev Allerg Immunol. 2018;55(3):271–94.
8 Mease PJ, Gladman DD, Papp KA, Khraishi MM, Thaçi D, Behrens F, et al. Prevalence of rheumatologist-diagnosed psoriatic arthritis in patients with psoriasis in European/North American dermatology clinics. J Am Acad Dermatol. 2013;69(5):729–35.
9 Schmidt A, Glimm AM, Haugen IK, Hoff P, Schmittat G, Burmester GR, et al. Detection of subclinical skin manifestation in patients with psoriasis and psoriatic arthritis by fluorescence optical imaging. Arthritis Res Ther. 2020;22(1):192.
10 Ocampo DV, Gladman D. Psoriatic arthritis. F1000Res. 2019;8:F1000 Faculty Rev-1665.
11 Costa L, Perricone C, Chimenti MS, Del Puente A, Caso P, Peluso R, et al. Switching between biological treatments in psoriatic arthritis: a review of the evidence. Drugs R D. 2017;17(4):509–22.
12 Kavanaugh A, Coates LC, van der Windt DA, Corp N, Soriano ER. GRAPPA treatment recommendations: updates and methods. J Rheumatol Suppl. 2020;96:41–5.
13 Ghoreschi K, Balato A, Enerbäck C, Sabat R. Therapeutics targeting the IL-23 and IL-17 pathway in psoriasis. Lancet. 2021;397(10275):754–766.
14 McInnes IB, Kavanaugh A, Gottlieb AB, Puig L, Rahman P, Ritchlin C, et al. Efficacy and safety of ustekinumab in patients with active psoriatic arthritis: 1 year results of the phase 3, multicentre, double-blind, placebo-controlled PSUMMIT 1 trial. Lancet. 2013;382(9894):780–9.
15 Ritchlin C, Rahman P, Kavanaugh A, McInnes IB, Puig L, Li S, et al. Efficacy and safety of the anti-IL-12/23 p40 monoclonal antibody, ustekinumab, in patients with active psoriatic arthritis despite conventional non-biological and biological anti-tumour necrosis factor therapy: 6-month and 1-year results of the phase 3, multicentre, double-blind, placebo-controlled, randomised PSUMMIT 2 trial. Ann Rheum Dis. 2014;73(6):990–9.
16 Deodhar A, Helliwell PS, Boehncke WH, Kollmeier AP, Hsia EC, Subramanian RA, et al. Guselkumab in patients with active psoriatic arthritis who were biologic-naive or had previously received TNFα inhibitor treatment (DISCOVER-1): a double-blind, randomised, placebo-controlled phase 3 trial. Lancet. 2020;395(10230):1115–25.

17 TREMFYA® (guselkumab) approved by U.S. Food and Drug Administration as the first selective interlukin (IL)-23 inhibitor for active psoriatic arthritis [press release, Internet]. [cited Jul 14, 2020]. Available from: https://www.jnj.com/tremfya-guselkumab-approved-by-u-s-food-and-drug-administration-as-the-first-selective-interleukin-il-23-inhibitor-for-active-psoriatic-arthritis.
18 Mease PJ, Rahman P, Gottlieb AB, Kollmeier AP, Hsia EC, Xu XL, et al. Guselkumab in biologic-naive patients with active psoriatic arthritis (DISCOVER-2): a double-blind, randomised, placebo-controlled phase 3 trial. Lancet. 2020;395(10230):1126–36.
19 Megna M, Balato A, Napolitano M, Gallo L, Caso F, Costa L, et al. Psoriatic disease treatment nowadays: unmet needs among the "jungle of biologic drugs and small molecules". Clin Rheumatol. 2018;37(7):1739–41.
20 Russell CB, Rand H, Bigler J, Kerkof K, Timour M, Bautista E, et al. Gene expression profiles normalized in psoriatic skin by treatment with brodalumab, a human anti-IL-17 receptor monoclonal antibody. J Immunol. 2014;192(8):3828–36.
21 Frieder J, Kivelevitch D, Menter A. Secukinumab: a review of the anti-IL-17A biologic for the treatment of psoriasis. Ther Adv Chronic Dis. 2018;9(1):5–21.
22 Syed YY. Ixekizumab: A review in moderate to severe plaque psoriasis. Am J Clin Dermatol. 2017;18(1):147–58.
23 European Medicines Agency. Summary of product characteristics: Kyntheum 210 mg solution for injection in pre-filled syringe [Internet]. 2017. Available from: https://www.ema.europa.eu/en/documents/product-information/kyntheum-epar-product-information_en.pdf.
24 Valeant Pharmaceuticals Inc. Prescribing information: SILIQTM (brodalumab) injection for subcutaneous use [Internet]. 2017. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761032lbl.pdf.
25 LUMICEF® approved in Japan [press release, Internet]. [Jul 4, 2016]. Available from: https://www.kyowakirin.com/media_center/news_releases/2016/e20160704_01.html.
26 Lebwohl M, Strober B, Menter A, Gordon K, Weglowska J, Puig L, et al. Phase 3 studies comparing brodalumab with ustekinumab in psoriasis. N Engl J Med. 2015;373(14):1318–28.
27 Mease PJ, Helliwell PS, Hjuler KF, Raymond K, McInnes I. Brodalumab in psoriatic arthritis: results from the randomised phase III AMVISION-1 and AMVISION-2 trials. Ann Rheum Dis. 2021;80(2):185–93.
28 Fredriksson T, Pettersson U. Severe psoriasis – oral therapy with a new retinoid. Dermatologica. 1978;157(4):238–44.
29 Bushnell DM, Martin ML, McCarrier K, Gordon K, Chiou CF, Huang X, et al. Validation of the Psoriasis Symptom Inventory (PSI), a patient-reported outcome measure to assess psoriasis symptom severity. J Dermatolog Treat. 2013;24(5):356–60.
30 Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI) – a simple practical measure for routine clinical use. Clin Exp Dermatol. 1994;19(3):210–6.
31 Aalen OO, Johansen S. An empirical transition matrix for non-homogeneous Markov chains based on censored observations. Scan J Stat. 1978;5:141–50.
32 Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc. 1999;94(446):496–509.
33 Gray RJ. A class of K-sample tests for comparing the cumulative incidence of a competing risk. Ann Statist. 1988;16:1141–54.
34 Coates LC, Kavanaugh A, Mease PJ, Soriano ER, Laura Acosta-Felquer M, Armstrong AW, et al. Group for Research and Assessment of Psoriasis and Psoriatic Arthritis 2015 treatment recommendations for psoriatic arthritis. Arthritis Rheumatol. 2016;68(5):1060–71.
35 Armstrong AW, Feldman SR, Korman NJ, Meng X, Guana A, Nyirady J, et al. Assessing the overall benefit of a medication: cumulative benefit of secukinumab over time in patients with moderate-to-severe plaque psoriasis. J Dermatolog Treat. 2017;28(3):200–5.
36 Warren RB, Hansen JB, Reich K, Paul C, Puig L. Complete clearance and psoriasis area and severity index response for brodalumab and ustekinumab in AMAGINE-2 and -3. J Eur Acad Dermatol Venereol. 2021;35(2):450–7.
37 Feldman SR, Bushnell DM, Klekotka PA, Scanlon M, Martin ML, Wade SW, et al. Differences in psoriasis signs and symptom severity between patients with clear and almost clear skin in clinical practice. J Dermatolog Treat. 2016;27(3):224–7.
38 Girolomoni G, Griffiths CE, Krueger J, Nestle FO, Nicolas JF, Prinz JC, et al. Early intervention in psoriasis and immune-mediated inflammatory diseases: A hypothesis paper. J Dermatolog Treat. 2015;26(2):103–12.
39 Lacour JP, Bewley A, Hammond E, Hansen JB, Horne L, Paul C, et al. Association between patient- and physician-reported outcomes in patients with moderate-to-severe plaque Psoriasis treated with Biologics in Real Life (PSO-BIO-REAL). Dermatol Ther (Heidelb). 2020;10(5):1099–109.
40 Revicki DA, Willian MK, Menter A, Saurat JH, Harnam N, Kaul M. Relationship between clinical response to therapy and health-related quality of life outcomes in patients with moderate to severe plaque psoriasis. Dermatology. 2008;216(3):260–70.
41 Takeshita J, Callis Duffin K, Shin DB, Krueger GG, Robertson AD, Troxel AB, et al. Patient-reported outcomes for psoriasis patients with clear versus almost clear skin in the clinical setting. J Am Acad Dermatol. 2014;71(4):633–41.
42 Viswanathan HN, Chau D, Milmont CE, Yang W, Erondu N, Revicki DA, et al. Total skin clearance results in improvements in health-related quality of life and reduced symptom severity among patients with moderate to severe psoriasis. J Dermatolog Treat. 2015;26(3):235–9.
43 Uhlenhake EE, Kurkowski D, Feldman SR. Conversations on psoriasis – what patients want and what physicians can provide: a qualitative look at patient and physician expectations. J Dermatolog Treat. 2010;21(1):6–12.
44 Warren RB, Gooderham M, Burge R, Zhu B, Amato D, Liu KH, et al. Comparison of cumulative clinical benefits of biologics for the treatment of psoriasis over 16 weeks: Results from a network meta-analysis. J Am Acad Dermatol. 2020;82(5):1138–49.
45 Krakowski P, Gerkowicz A, Pietrzak A, Krasowska D, Jurkiewicz A, Gorzelak M, et al. Psoriatic arthritis – new perspectives. Arch Med Sci. 2019;15(3):580–9.
46 Raychaudhuri SP, Wilken R, Sukhov AC, Raychaudhuri SK, Maverakis E. Management of psoriatic arthritis: early diagnosis, monitoring of disease severity and cutting edge therapies. J Autoimmun. 2017;76:21–37.
47 Haroon M, Gallagher P, FitzGerald O. Diagnostic delay of more than 6 months contributes to poor radiographic and functional outcome in psoriatic arthritis. Ann Rheum Dis. 2015;74(6):1045–50.
48 Girolomoni G, Gisondi P. Psoriasis and systemic inflammation: underdiagnosed enthesopathy. J Eur Acad Dermatol Venereol. 2009;23(Suppl 1):3–8.

4. Diskussion

Die Fortschritte im Verständnis der Immunpathogenese von Psoriasis hat zur Identifizierung von neuen Therapiezielen geführt. Die Entwicklung von gezielten Therapien gegen die verschiedenen pathogenetischen Ansatzpunkte stellt personalisierte Therapiekonzepte für Psoriasispatienten:innen basierend auf Patientencharakteristika, Psoriasismanifestationen oder Begleiterkrankungen bereit.

Die TNFα-Inhibitoren waren die ersten gezielten Therapien der Psoriasis, die durch die Blockade von TNFα eine hervorragende Wirksamkeit an der Plaque-Psoriasis, Nagelpsoriasis, Psoriasis Arthritis und axiale Spondyloarthritis gezeigt haben (10, 56, 57). Infliximab war der erste chimäre monoklonale Antikörper gegen TNFα. Infliximab brachte die Revolution in der Psoriasistherapie mit einer ca. 90% durchschnittlichen Besserung des PASI-Scores nach 10 Wochen (58). Außer den immunologischen Effekten durch die Inhibition vom TNFα-Signalling zeigte sich eine Normalisierung der apoptotischen Balance der psoriatischen Keratinozyten unter der Therapie mit Infliximab (24, 58). Die Einschränkung der intravenösen Verabreichung von Infliximab konnte durch die Entwicklung von Etanercept, Adalimumab, Golimumab und Certolizumab-pegol als subkutan applizierbare TNFα-Inhibitoren aufgehoben werden (10).

Trotz der guten Wirksamkeit mit einem günstigen Sicherheitsprofil weisen die TNFα-Inhibitoren klassenspezifische Nebenwirkungen, wie Tuberkulose oder Malignitäten insbesondere Plattenepithelkarzinome (PEC) auf (10). Die lichtinduzierten Hauttumore sind bei den Psoriasispatienten:innen besonders häufig. In einer großen Kohorte konnte eine Prävalenz von Hautkrebs von 3.5% in Psoriasispatienten:innen vs. 0.8% bei der Kontrollgruppe nachgewiesen werden. Davon betrafen 2.8% den nicht-melanozytären Hautkrebs (59). Der Grund dafür könnten die intensive UV-Exposition i.R. der Phototherapie für die Psoriasis oder die langzeitige Vortherapie mit Ciclosporin A sein. Um die pathogenetische Rolle des TNFα in der Viabilität von malignen Keratinozyten zu beleuchten und den Einfluss dessen Inhibition auf die apoptotischen Effekte vom 5-Fluoruracil (5FU) als Standardzytostatikum bei PEC zu untersuchen, induzierten wir endogene und exogene apoptotische Wege in PNHK, HaCaT und SCC-13 Zellen. TNFα zeigte einen synergistischen Effekt der apoptotischen Stimuli von TRAIL und 5FU in den malignen Keratinozyten. Die Synergie konnte durch die Blockade von TNFα mittels Infliximab aufgehoben werden.

Außerdem wurde der apoptotische Effekt von 5FU an der PNHK durch den TNFα abgeschwächt (60). Das 5FU ist eine gut etablierte Chemotherapie für aktinische Keratosen bzw. PEC, die sowohl topisch als auch systemisch verabreicht wird (61, 62). Diese Ergebnisse deuten auf die Wichtigkeit der Anwesenheit von TNFα für das Therapieansprechen von 5FU bei malignen Tumoren der Keratinozyten hin. Die Blockade von TNFα, beispielsweise mit Infliximab, könnte zu einem verminderten Therapieerfolg von 5FU bei Psoriasispatienten:innen mit solchen Tumoren führen.

Trotz möglicher Nebenwirkungen ist das Sicherheitsprofil von TNFα-Inhibitoren günstig und sind mit ihrem Ansatz in der Psoriasis und derer Komorbiditäten besonders bedeutsam. Zudem sind TNFα-Inhibitoren bei Nagelpsoriasis und Psoriasis Arthritis sehr wirksam (10). In einer prospektiven nicht-interventionellen Studie bei Psoriasispatienten:innen mit Nagelbeteiligung und gleichzeitiger PsA untersuchten wir die Wirksamkeit der ununterbrochenen Therapie mit Etanercept, Infliximab und Adalimumab über 2 Jahre. Die Inhibition von TNFα führte zu einer schnellen und anhaltenden Besserung der Plaque und Nagel-Psoriasis. Außerdem verbesserten sich die Arthritissymptome im Hinblick auf die Anzahl der geschwollenen und druckschmerzhaften Gelenke. Zusätzlich wurde eine konstante Besserung der Lebensqualität (DLQI) und des Gesundheitsstatus (HAQ) der Patienten beobachtet. Bereits 3 Monate nach der Einleitung der Therapie erreichten die Patienten das Funktionalitätsziel für die Kontrolle der Erkrankung (HAQ<0.5) (57). Die Indikation zur Therapie wurde nach dermatologischen Kriterien gestellt und die Patienten wurden ausschließlich von Dermatologen betreut. In der untersuchten Kohorte wurde auch die PsA ausreichend therapiert. Für die Optimierung der Therapie der PsA und für die Etablierung der Therapieentscheidung von Dermatologen wurde ein interdisziplinäres Konsenspaper veröffentlicht. Eine Therapie mit TNFα-Inhibitoren wird bei Psoriasispatienten:innen mit PsA, Enthesitis, Daktylitis oder axiale Spondylarthritis empfohlen (63).

Adalimumab war der erste monoklonale Antikörper gegen TNFα als sc Applikation für die Therapie der Plaque-Typ Psoriasis. Mehr als die Hälfte der Patienten erreichen unter Adalimumab eine 90% Verbesserung des PASI-Scores nach 16 Wochen im Vergleich zu 13.6% der Patienten unter MTX (64). Die Wirksamkeit von Adalimumab an der Nagelpsoriasis nach 52 Monaten Therapie wurde in einer Phase 3 placebo-kontrollierten Studie nachgewiesen. Nach einem Jahr Therapie mit Adalimumab

erreichten ca. 65% der Patienten eine 75%ige Besserung der Nagelpsoriasis (NAPSI75) (65). Darüber hinaus untersuchten wir die Wirksamkeit von Adalimumab an der Psoriasis der Nagelmatrix und des Nagelbettes über eine Therapiedauer von 2 Jahren. Sowohl die Nagelmatrix als auch das Nagelbett von Patienten mit Nagelpsoriasis verbesserten sich signifikant innerhalb von 3 Monaten. Interessanterweise waren ein jüngeres Probandenalter (≤47 Jahre) als das Durchschnittalter der Kohorte und ein erhöhter BMI begünstigende Prädiktoren für das bessere Ansprechen auf die Therapie. Das Geschlecht zeigte keinen relevanten Einfluss auf den Therapieerfolg. Auch die Lebensqualität der Patienten:innen mit Nagelpsoriasis verbesserte sich unter der Therapie mit Adalimumab und korrelierte signifikant mit dem NAPSI-Score nach 12 Monaten Therapie (56). Nagelpsoriasis ist mit schlechter Lebensqualität, psychologischem Stress und Verlegenheit assoziiert (66). Auch die Funktionalität der Patienten mit Nagelpsoriasis ist im Alltag eingeschränkt (67). Aufgrund des schlechten Ansprechens der Lokaltherapien und der Belastung der Patienten gehört die Nagelpsoriasis zu den besonderen Lokalisationen der Psoriasis für die Eskalierung der Therapie von topisch auf systemisch (68). Adalimumab bietet eine vielversprechende Therapieoption für Patienten mit Nagelpsoriasis.

Die Entwicklung von neuen Klassen von Biologika nach den TNFα-Inhibitoren ermöglicht höhere Therapieerfolge mit einem besseren Sicherheitsprofil. Ustekinumab, als einziger p40-Inhibitor, ist sowohl für die Plaque-Typ Psoriasis als auch für die PsA in einer körpergewichtsadaptierten Dosierung zugelassen (43, 69). Die Häufigkeit von Infektionen und auch von den Malignitäten von Keratinozyten unter der Therapie mit Ustekinumab ist deutlich geringer im Vergleich zu den TNFα-Inhibitoren (43). Noch wirksamer als Ustekinumab oder TNFα-Inhibitoren sowohl für den Plaque-Typ Psoriasis als auch für die PsA sind die IL-17-Antikörper (70, 71). Brolamumab ist ein humaner monoklonaler Antikörper, der selektiv den Rezeptor IL-17RA blockiert. Im Vergleich zu Ustekinumab zeigte Brodalumab eine schnellere und höhere Wirksamkeit bei Patienten mit Plaque-Typ Psoriasis (72). Die Wirksamkeit von Brodalumab bei PsA, Enthesitis und Daktylitis konnte ebenfalls in einer placebo-kontrollierten Phase 3 Studie bewiesen werden (73). In einer *post hoc* Analyse der Phase 3 Studien von Brodalumab (72) haben wir die Wirksamkeit von Brodalumab vs. Ustekinumab bei der Plaque-Typ Psoriasis von Patienten mit begleitender PsA verglichen. Brodalumab zeigte eine höhere Wirksamkeit bei der Plaque-Typ

Psoriasis, eine schnellere Besserung der Lebensqualität und eine signifikantere Linderung der Psoriasissymptome im Vergleich zu Ustekinumab für die gesamte Beobachtungsdauer unabhängig von einer gleichzeitigen PsA (74). Diese Ergebnisse können von Bedeutung sein, wenn Dermatologen bei Psoriasispatienten:innen mit begleitender PsA die Therapieentscheidung treffen sollen. Üblicherweise folgt die Manifestation der PsA einer bereits vorbekannten Plaque-Typ Psoriasis. Bei ca. 67% der Patienten tritt die PsA erst 10-20 Jahre nach der Erstmanifestation der Pso auf (75). Aus diesem Grund sind häufig die Dermatologen die ersten Behandler, die eine PsA diagnostizieren und entsprechend therapieren. Die überlappende Pathogenese der Pso und PsA hat, mit der Ausnahme von Fumarsäureestern und Ciclosporin A, zu der Entwicklung von gemeinsamen Therapien geführt. Abhängig von der Manifestation, die im Vordergrund steht, Pso oder PsA, kann die Therapie entsprechend ausgewählt werden. In einer head-to-head Phase-3-Studie mit kombinierten Endpunkten, wurde gezeigt, dass Ixekizumab besser als Adalimumab wirkte, wenn die Pso im Vordergrund stand (Ziel PASI100). Im Gegensatz dazu war die Wirkung von Ixekizumab nicht überlegen bei Patienten mit ausgeprägter Plaque-Typ Psoriasis und gleichzeitiger aktiver PsA (Ziel PASI100 und ACR50) (76).

Nach aktuellen Studiendaten konsumiert ein Drittel der Psoriasispatienten:innen übermäßig Alkohol. Nebst der erhöhten Prävalenz von Depression, Angststörung und psychologischen Störung ist die alkoholassoziierte Mortalität der Psoriasispatienten:innen im Vergleich zu der gesunden Bevölkerung deutlich erhöht. Psoriasispatienten:innen konsumieren Alkohol, um den psychologischen Stress zu kompensieren (77). Abermals kann Alkoholkonsum zu einer Verschlechterung der Pso führen. Zudem wird Alkoholabusus von mehr als 80mg/Tag mit einem schlechteren Therapieansprechen assoziiert (78). Außer Alkohol kann Nikotin ebenfalls das Erstauftreten und den Verlauf der Psoriasis beeinflussen. Nicht nur die Adhärenz der Patienten an die Therapien, sondern auch das Therapieansprechen können durch den Nikotinabusus beeinträchtigt werden (79, 80). In ähnlicher Weise zählt der erhöhte BMI bzw. die Adipositas als Risikofaktor für die Psoriasis. Adipositas wird mit schwerer Psoriasis assoziiert (81). Für die Auswahl der passenden Therapien in der Alltagpraxis sind solche gravierenden Faktoren entscheidend. Wir untersuchten den Einfluss des Vorhandenseins von keinem, einem, zweien oder allen dreien Faktoren auf das Therapieansprechen von Ustekinumab oder Brodalumab in einer Subanalyse der Phase-3-Studien AMAGINE-

2 und -3. In allen vier Szenarien war die Therapie mit Brodalumab deutlich wirksamer als Ustekinumab. Eine signifikant höhere Anzahl von Patienten in der Brodalumabgruppe erreichte eine komplette Remission der Plaque-Typ Psoriasis. Auch die Verbesserung der Lebensqualität der Patienten und die Linderung von Psoriasissymptomen waren signifikant höher im Brodalumab-Arm unabhängig von dem Vorhandensein der untersuchten Risikofaktoren (82).

5. Zusammenfassung

Durch die Fortschritte im Verständnis der Immunpathogenese der Psoriasis wurden neue hochwirksame und sichere gezielte Therapien entwickelt. Diese neuen Therapien ermöglichen individuelle Therapiekonzepte für die Betroffenen. Solche personalisierten Therapien garantieren die höchste Wirksamkeit mit den geringsten Nebenwirkungen für die Patienten in der Zusammenschau von demographischen Daten, Schweregrad und klinischen Manifestationen der Psoriasis sowie Begleiterkrankungen. Genetische oder laborchemische Biomarker vereinfachen die zeitnahe Diagnosestellung und dementsprechend die Auswahl der richtigen Therapie, wie z.B. im Falle der rheumatoiden Arthritis, oder zeigen eine prognostische Bedeutung wie beim Melanom (83, 84). Aufgrund des Mangels solcher Biomarker bei der Psoriasis ist das klinische Profiling von Patienten für die Auswahl der geeigneten Therapie besonders wegweisend. In dieser wissenschaftlichen Arbeit untersuchten wir drei verschiedene Klassen von Biologika als gezielte Therapien für Psoriasis bei Patienten mit verschiedenen Charakteristika und empfehlen möglichst passende Szenarien für die Therapieentscheidung.

Die TNFα-Inhibitoren sind die ersten gezielten Therapien für Psoriasis. Die ersten klinischen Daten wurden an Patient:innen mit PsA erhoben und dementsprechend die erste Zulassungsindikation vergeben. Außer der PsA sprechen auch andere Manifestationen der Psoriasis auf die Therapie mit TNFα-Inhibitoren hervorragend an. In unserer Studie mit Psoriasispatient:innen mit gleichzeitiger PsA und Nagelpsoriasis führte die Therapie mit Etanercept, Adalimumab und Infliximab zu einer raschen Verbesserung der Nagelpsoriasis und der Arthritissymptomatik. Deshalb kann eine anti-TNFα Therapie bei Patienten:innen mit ausgeprägter Nagelpsoriasis und PsA empfohlen werden. Diese Patienten können von Dermatologen therapiert und monitoriert werden.

Zu einer weiteren Prüfung der Wirksamkeit von TNFα-Inhibitoren bei Nagelpsoriasis schlossen wir Patienten:innen mit Plaque-Typ Psoriasis und gleichzeitiger Nagelpsoriasis in einer nicht-interventionellen Studie mit Adalimumab ein. Sowohl die Nagelpsoriasis als auch die Lebensqualität der Patienten:innen verbesserten sich signifikant innerhalb von 3 Monaten. Diese Resultate bestätigen die Ergebnisse von kontrollierten Studien bis 52 Wochen in einem Real-World Setting über 2 Jahre.

Adalimumab ist eine geeignete langfristige Therapie für Patienten:innen mit ausgeprägter Nagelpsoriasis.

Psoriasispatienten:innen sind aufgrund von langzeitiger UV-Exposition von NMSC oder auch Melanomen gefährdet (59). Klinische Daten zur Wirksamkeit und Sicherheit von TNFα-Inhibitoren bei Patienten:innen mit Psoriasis oder PsA zeigen ein erhöhtes Risiko für beide Formen von Hautkrebs und v.a. für die aktinischen Keratosen bzw. Plattenepithelkarzinome. In einem in vitro Simulationsmodell mit PNHK und SCC-Zellen konnten wir die entscheidende Rolle von TNFα bei der Apoptose von malignen Keratinozyten unter der Therapie mit 5FU zeigen. Diese Ereignisse waren unter der Blockade des TNFα mit Infliximab reversibel. Im Zusammenhang mit unseren in vitro Befunden und den vorhandenen klinischen Daten wäre eine Therapie mit anti-TNFα Antikörpern bei Patienten mit solchen Hauttumoren oder mit Risikofaktoren für NMSC nicht zu empfehlen. Eine sicherere Alternative zu diesen Therapien bzgl. NMSC stellen die neuen Klassen von Biologika, anti-p40, anti-IL-17 und anti-p19, dar.

Übereinstimmend mit den TNFα-Inhibitoren sind die neuen Klassen, anti-p40 und anti-IL-17, sowohl bei der Plaque-Typ Psoriasis als auch bei der PsA gut wirksam. Besonders gut ist das Ansprechen der kutanen Manifestation der Psoriasis auf solche Therapien, sodass eine 90%ige bzw. 100%ige Besserung der Plaque-Typ Psoriasis erreicht werden kann. In einer Metanalyse der kontrollierten Studien AMAGINE-2 und -3 untersuchten wir die Wahrscheinlichkeit, eine komplette Remission der Plaque-Typ Psoriasis bei Patiennten:innen mit oder ohne PsA unter Brodalumab vs. Ustekinumab zu erreichen. Die Überlegenheit der Therapie mit Brodalumab war signifikant bemerkbar gegenüber Ustekinumab unabhängig von einer gleichzeitigen PsA. Auch die Psoriasis-Symptome und die Lebensqualität der Patienten war unter Brodalumab signifikant besser. Somit kann beschlossen werden, dass Brodalumab deutlich wirksamer ist bei Psoriasispatienten:innen unabhängig vom Vorhandensein einer PsA.

Der Einfluss von Nikotinabusus, Alkoholkonsum und Übergewicht bzw. Adipositas als Negativfaktoren für den Schweregrad und das Therapieansprechen der Psoriasis ist längst nachgewiesen. In einer Subanalyse der kontrollierten Studien AMAGINE-2 und -3 konnten wir zeigen, dass signifikant mehr Patienten:innen mit keinem, einem, zweien oder allen dieser Lebensstil-Faktoren eine komplette Remission der Plaque-

Typ Psoriasis unter Brodalumab vs. Ustekinumab erreicht haben. In diesem Sinne, wäre die Therapie mit Brodalumab bei Patienten:innen mit diesen Gewohnheiten empfehlenswert.

Zusammenfassend ist das Ziel dieser Arbeit die Unterstützung der Therapieentscheidung bei Psoriasispatienten:innen mit besonderen Manifestationen oder erschwerenden Lebensstil-Faktoren basierend auf einem klinischen Profiling. Die Entwicklung von weiteren gezielten Therapien, wie IL-23-Antikörper oder TYK2-Inhibitoren, erweitert das Spektrum der verfügbaren Therapien und fördert präzisere personalisierte Therapiekonzepte.

6. Literaturverzeichnis

1. Schett G, Rahman P, Ritchlin C, McInnes IB, Elewaut D, Scher JU. Psoriatic arthritis from a mechanistic perspective. Nat Rev Rheumatol. 2022;18(6):311-25.
2. Boehncke WH, Schon MP. Psoriasis. Lancet. 2015;386(9997):983-94.
3. Fredriksson T, Pettersson U. Severe psoriasis--oral therapy with a new retinoid. Dermatologica. 1978;157(4):238-44.
4. Rich P, Scher RK. Nail Psoriasis Severity Index: a useful tool for evaluation of nail psoriasis. J Am Acad Dermatol. 2003;49(2):206-12.
5. Gelfand JM, Feldman SR, Stern RS, Thomas J, Rolstad T, Margolis DJ. Determinants of quality of life in patients with psoriasis: a study from the US population. J Am Acad Dermatol. 2004;51(5):704-8.
6. Mattei PL, Corey KC, Kimball AB. Psoriasis Area Severity Index (PASI) and the Dermatology Life Quality Index (DLQI): the correlation between disease severity and psychological burden in patients treated with biological therapies. J Eur Acad Dermatol Venereol. 2014;28(3):333-7.
7. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)--a simple practical measure for routine clinical use. Clin Exp Dermatol. 1994;19(3):210-6.
8. Scher JU, Ogdie A, Merola JF, Ritchlin C. Preventing psoriatic arthritis: focusing on patients with psoriasis at increased risk of transition. Nat Rev Rheumatol. 2019;15(3):153-66.
9. Gelfand JM, Gladman DD, Mease PJ, Smith N, Margolis DJ, Nijsten T, et al. Epidemiology of psoriatic arthritis in the population of the United States. J Am Acad Dermatol. 2005;53(4):573.
10. Greb JE, Goldminz AM, Elder JT, Lebwohl MG, Gladman DD, Wu JJ, et al. Psoriasis. Nat Rev Dis Primers. 2016;2:16082.
11. Mease PJ, Gladman DD, Papp KA, Khraishi MM, Thaci D, Behrens F, et al. Prevalence of rheumatologist-diagnosed psoriatic arthritis in patients with psoriasis in European/North American dermatology clinics. J Am Acad Dermatol. 2013;69(5):729-35.
12. Reich K, Kruger K, Mossner R, Augustin M. Epidemiology and clinical pattern of psoriatic arthritis in Germany: a prospective interdisciplinary epidemiological study of 1511 patients with plaque-type psoriasis. Br J Dermatol. 2009;160(5):1040-7.
13. Gladman DD, Antoni C, Mease P, Clegg DO, Nash P. Psoriatic arthritis: epidemiology, clinical features, course, and outcome. Ann Rheum Dis. 2005;64 Suppl 2:ii14-7.
14. Wilson FC, Icen M, Crowson CS, McEvoy MT, Gabriel SE, Kremers HM. Incidence and clinical predictors of psoriatic arthritis in patients with psoriasis: a population-based study. Arthritis Rheum. 2009;61(2):233-9.
15. Taylor W, Gladman D, Helliwell P, Marchesoni A, Mease P, Mielants H, et al. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum. 2006;54(8):2665-73.
16. Buttner J, Glimm AM, Kokolakis G, Erdmann-Keding M, Burmester GR, Hoff P, et al. Follow-Up Comparison of Fluorescence Optical Imaging With Musculoskeletal Ultrasound for Early Detection of Psoriatic Arthritis. Front Med (Lausanne). 2022;9:845545.
17. Haroon M, Gallagher P, FitzGerald O. Diagnostic delay of more than 6 months contributes to poor radiographic and functional outcome in psoriatic arthritis. Ann Rheum Dis. 2015;74(6):1045-50.
18. Torres MI, Rios A. Current view of the immunopathogenesis in inflammatory bowel disease and its implications for therapy. World J Gastroenterol. 2008;14(13):1972-80.
19. Cohen AD, Dreiher J, Birkenfeld S. Psoriasis associated with ulcerative colitis and Crohn's disease. J Eur Acad Dermatol Venereol. 2009;23(5):561-5.
20. Wolk K, Sabat R. Adipokines in psoriasis: An important link between skin inflammation and metabolic alterations. Rev Endocr Metab Disord. 2016;17(3):305-17.
21. Gerdes S, Mrowietz U, Boehncke WH. [Comorbidity in psoriasis]. Hautarzt. 2016;67(6):438-44.
22. Gelfand JM, Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB. Risk of myocardial infarction in patients with psoriasis. JAMA. 2006;296(14):1735-41.

23. Jing D, Xiao H, Shen M, Chen X, Han X, Kuang Y, et al. Association of Psoriasis With Anxiety and Depression: A Case-Control Study in Chinese Patients. Front Med (Lausanne). 2021;8:771645.
24. Kokolakis G, Giannikaki E, Stathopoulos E, Avramidis G, Tosca AD, Kruger-Krasagakis S. Infliximab restores the balance between pro- and anti-apoptotic proteins in regressing psoriatic lesions. Br J Dermatol. 2012;166(3):491-7.
25. Nestle FO, Kaplan DH, Barker J. Psoriasis. N Engl J Med. 2009;361(5):496-509.
26. Clot J, Charmasson E, Massip H, Guilhou JJ, Meynadier J. [Letter: Deficit of T-lymphocytes in psoriasis]. Nouv Presse Med. 1975;4(28):2039-40.
27. Sabat R, Philipp S, Hoflich C, Kreutzer S, Wallace E, Asadullah K, et al. Immunopathogenesis of psoriasis. Exp Dermatol. 2007;16(10):779-98.
28. Sajja AP, Joshi AA, Teague HL, Dey AK, Mehta NN. Potential Immunological Links Between Psoriasis and Cardiovascular Disease. Front Immunol. 2018;9:1234.
29. Kokolakis G, Panagis L, Stathopoulos E, Giannikaki E, Tosca A, Kruger-Krasagakis S. From the protein to the graph: how to quantify immunohistochemistry staining of the skin using digital imaging. J Immunol Methods. 2008;331(1-2):140-6.
30. Arican O, Aral M, Sasmaz S, Ciragil P. Serum levels of TNF-alpha, IFN-gamma, IL-6, IL-8, IL-12, IL-17, and IL-18 in patients with active psoriasis and correlation with disease severity. Mediators Inflamm. 2005;2005(5):273-9.
31. Perez C, Albert I, DeFay K, Zachariades N, Gooding L, Kriegler M. A nonsecretable cell surface mutant of tumor necrosis factor (TNF) kills by cell-to-cell contact. Cell. 1990;63(2):251-8.
32. Li H, Lin X. Positive and negative signaling components involved in TNFalpha-induced NF-kappaB activation. Cytokine. 2008;41(1):1-8.
33. Ghoreschi K, Balato A, Enerback C, Sabat R. Therapeutics targeting the IL-23 and IL-17 pathway in psoriasis. Lancet. 2021;397(10275):754-66.
34. Schett G, Lories RJ, D'Agostino MA, Elewaut D, Kirkham B, Soriano ER, et al. Enthesitis: from pathophysiology to treatment. Nat Rev Rheumatol. 2017;13(12):731-41.
35. Veale DJ, Fearon U. The pathogenesis of psoriatic arthritis. Lancet. 2018;391(10136):2273-84.
36. Nast A, Altenburg A, Augustin M, Boehncke WH, Harle P, Klaus J, et al. German S3-Guideline on the treatment of Psoriasis vulgaris, adapted from EuroGuiDerm - Part 1: Treatment goals and treatment recommendations. J Dtsch Dermatol Ges. 2021;19(6):934-150.
37. Korber A, Wilsmann-Theis D, Augustin M, von Kiedrowski R, Mrowietz U, Rosenbach T, et al. Topische Therapie bei Psoriasis vulgaris - ein Behandlungspfad. J Dtsch Dermatol Ges. 2019;17 Suppl 4:3-14.
38. Morrison PJ, Suhrkamp I, Gerdes S, Mrowietz U. Oral dimethyl fumarate induces changes within the peripheral neutrophil compartment of patients with psoriasis that are linked with skin improvement. Br J Dermatol. 2021;185(3):605-15.
39. Mrowietz U, Szepietowski JC, Loewe R, van de Kerkhof P, Lamarca R, Ocker WG, et al. Efficacy and safety of LAS41008 (dimethyl fumarate) in adults with moderate-to-severe chronic plaque psoriasis: a randomized, double-blind, Fumaderm((R)) - and placebo-controlled trial (BRIDGE). Br J Dermatol. 2017;176(3):615-23.
40. Warren RB, Mrowietz U, von Kiedrowski R, Niesmann J, Wilsmann-Theis D, Ghoreschi K, et al. An intensified dosing schedule of subcutaneous methotrexate in patients with moderate to severe plaque-type psoriasis (METOP): a 52 week, multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2017;389(10068):528-37.
41. Philipp S, Kokolakis G, Sabat R. [Systemic treatments for psoriasis and psoriatic arthritis]. Hautarzt. 2016;67(6):464-71.
42. Heydendael VM, Spuls PI, Opmeer BC, de Borgie CA, Reitsma JB, Goldschmidt WF, et al. Methotrexate versus cyclosporine in moderate-to-severe chronic plaque psoriasis. N Engl J Med. 2003;349(7):658-65.
43. Leonardi CL, Kimball AB, Papp KA, Yeilding N, Guzzo C, Wang Y, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week

results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). Lancet. 2008;371(9625):1665-74.
44. McInnes IB, Kavanaugh A, Gottlieb AB, Puig L, Rahman P, Ritchlin C, et al. Efficacy and safety of ustekinumab in patients with active psoriatic arthritis: 1 year results of the phase 3, multicentre, double-blind, placebo-controlled PSUMMIT 1 trial. Lancet. 2013;382(9894):780-9.
45. Strober BE, Crowley JJ, Yamauchi PS, Olds M, Williams DA. Efficacy and safety results from a phase III, randomized controlled trial comparing the safety and efficacy of briakinumab with etanercept and placebo in patients with moderate to severe chronic plaque psoriasis. Br J Dermatol. 2011;165(3):661-8.
46. Mosca M, Hong J, Hadeler E, Hakimi M, Liao W, Bhutani T. The Role of IL-17 Cytokines in Psoriasis. Immunotargets Ther. 2021;10:409-18.
47. Schinocca C, Rizzo C, Fasano S, Grasso G, La Barbera L, Ciccia F, et al. Role of the IL-23/IL-17 Pathway in Rheumatic Diseases: An Overview. Front Immunol. 2021;12:637829.
48. Sernicola A, Russo I, Alaibac M. Small-molecule-based immunotherapy for immunologically mediated skin conditions. Immunotherapy. 2020;12(6):417-29.
49. Kavanaugh A, Mease PJ, Gomez-Reino JJ, Adebajo AO, Wollenhaupt J, Gladman DD, et al. Longterm (52-week) results of a phase III randomized, controlled trial of apremilast in patients with psoriatic arthritis. J Rheumatol. 2015;42(3):479-88.
50. Papp K, Reich K, Leonardi CL, Kircik L, Chimenti S, Langley RG, et al. Apremilast, an oral phosphodiesterase 4 (PDE4) inhibitor, in patients with moderate to severe plaque psoriasis: Results of a phase III, randomized, controlled trial (Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis [ESTEEM] 1). J Am Acad Dermatol. 2015;73(1):37-49.
51. McInnes IB, Anderson JK, Magrey M, Merola JF, Liu Y, Kishimoto M, et al. Trial of Upadacitinib and Adalimumab for Psoriatic Arthritis. N Engl J Med. 2021;384(13):1227-39.
52. Mease P, Hall S, FitzGerald O, van der Heijde D, Merola JF, Avila-Zapata F, et al. Tofacitinib or Adalimumab versus Placebo for Psoriatic Arthritis. N Engl J Med. 2017;377(16):1537-50.
53. Bachelez H, van de Kerkhof PC, Strohal R, Kubanov A, Valenzuela F, Lee JH, et al. Tofacitinib versus etanercept or placebo in moderate-to-severe chronic plaque psoriasis: a phase 3 randomised non-inferiority trial. Lancet. 2015;386(9993):552-61.
54. Mease PJ, Deodhar AA, van der Heijde D, Behrens F, Kivitz AJ, Neal J, et al. Efficacy and safety of selective TYK2 inhibitor, deucravacitinib, in a phase II trial in psoriatic arthritis. Ann Rheum Dis. 2022;81(6):815-22.
55. Papp K, Gordon K, Thaci D, Morita A, Gooderham M, Foley P, et al. Phase 2 Trial of Selective Tyrosine Kinase 2 Inhibition in Psoriasis. N Engl J Med. 2018;379(14):1313-21.
56. Kokolakis G, Bachmann F, Wolk K, Sabat R, Philipp S. Efficacy of Adalimumab for Nail Psoriasis During 24 Months of Continuous Therapy. Acta Derm Venereol. 2020;100(14):adv00214.
57. Kokolakis G, Sabat R, Fischer I, Gomis-Kleindienst S, Fritz B, Burmester GR, et al. The Effect of TNF-alpha Inhibitors on Nail Psoriasis and Psoriatic Arthritis-Real-World Data from Dermatology Practice. J Pers Med. 2021;11(11).
58. Chaudhari U, Romano P, Mulcahy LD, Dooley LT, Baker DG, Gottlieb AB. Efficacy and safety of infliximab monotherapy for plaque-type psoriasis: a randomised trial. Lancet. 2001;357(9271):1842-7.
59. Herbosa CM, Hodges W, Mann C, Demehri S, Cornelius LA, Semenov YR. Risk of cancer in psoriasis: study of a nationally representative sample of the US population with comparison to a single-institution cohort. J Eur Acad Dermatol Venereol. 2020;34(9):e529-e31.
60. Kokolakis G, Sabat R, Kruger-Krasagakis S, Eberle J. Ambivalent Effects of Tumor Necrosis Factor Alpha on Apoptosis of Malignant and Normal Human Keratinocytes. Skin Pharmacol Physiol. 2021;34(2):94-102.
61. de Oliveira ECV, da Motta VRV, Pantoja PC, Ilha CSO, Magalhaes RF, Galadari H, et al. Actinic keratosis - review for clinical practice. Int J Dermatol. 2019;58(4):400-7.
62. Keil F, Hartl M, Altorjai G, Berghold A, Riedl R, Pecherstorfer M, et al. Docetaxel, cisplatin and 5-FU compared with docetaxel, cisplatin and cetuximab as induction chemotherapy in advanced

squamous cell carcinoma of the head and neck: Results of a randomised phase II AGMT trial. Eur J Cancer. 2021;151:201-10.
63. Gisondi P, Altomare G, Ayala F, Conti A, Dapavo P, De Simone C, et al. Consensus on the management of patients with psoriatic arthritis in a dermatology setting. J Eur Acad Dermatol Venereol. 2018;32(4):515-28.
64. Saurat JH, Stingl G, Dubertret L, Papp K, Langley RG, Ortonne JP, et al. Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis (CHAMPION). Br J Dermatol. 2008;158(3):558-66.
65. Elewski BE, Baker CS, Crowley JJ, Poulin Y, Okun MM, Calimlim B, et al. Adalimumab for nail psoriasis: efficacy and safety over 52 weeks from a phase-3, randomized, placebo-controlled trial. J Eur Acad Dermatol Venereol. 2019;33(11):2168-78.
66. Baran R. The burden of nail psoriasis: an introduction. Dermatology. 2010;221 Suppl 1:1-5.
67. de Jong EM, Seegers BA, Gulinck MK, Boezeman JB, van de Kerkhof PC. Psoriasis of the nails associated with disability in a large number of patients: results of a recent interview with 1,728 patients. Dermatology. 1996;193(4):300-3.
68. Mrowietz U, Kragballe K, Reich K, Spuls P, Griffiths CE, Nast A, et al. Definition of treatment goals for moderate to severe psoriasis: a European consensus. Arch Dermatol Res. 2011;303(1):1-10.
69. Gottlieb A, Menter A, Mendelsohn A, Shen YK, Li S, Guzzo C, et al. Ustekinumab, a human interleukin 12/23 monoclonal antibody, for psoriatic arthritis: randomised, double-blind, placebo-controlled, crossover trial. Lancet. 2009;373(9664):633-40.
70. Bilal J, Berlinberg A, Bhattacharjee S, Trost J, Riaz IB, Kurtzman DJB. A systematic review and meta-analysis of the efficacy and safety of the interleukin (IL)-12/23 and IL-17 inhibitors ustekinumab, secukinumab, ixekizumab, brodalumab, guselkumab and tildrakizumab for the treatment of moderate to severe plaque psoriasis. J Dermatolog Treat. 2018;29(6):569-78.
71. Gao Q, Zhao YX, Wang XJ, Shi J, Wang HM. Efficacy and safety of IL-17 inhibitors for patients with psoriatic arthritis: a systematic review and meta-analysis. Eur Rev Med Pharmacol Sci. 2021;25(7):2958-70.
72. Lebwohl M, Strober B, Menter A, Gordon K, Weglowska J, Puig L, et al. Phase 3 Studies Comparing Brodalumab with Ustekinumab in Psoriasis. N Engl J Med. 2015;373(14):1318-28.
73. Mease PJ, Helliwell PS, Hjuler KF, Raymond K, McInnes I. Brodalumab in psoriatic arthritis: results from the randomised phase III AMVISION-1 and AMVISION-2 trials. Ann Rheum Dis. 2021;80(2):185-93.
74. Kokolakis G, Vadstrup K, Hansen JB, Carrascosa JM. Brodalumab Is Associated with High Rates of Complete Clearance and Quality of Life Improvement: A Subgroup Analysis of Patients with Psoriasis and Concomitant Psoriatic Arthritis. Dermatology. 2022;238(4):620-9.
75. Mease P, Goffe BS. Diagnosis and treatment of psoriatic arthritis. J Am Acad Dermatol. 2005;52(1):1-19.
76. Mease PJ, Smolen JS, Behrens F, Nash P, Liu Leage S, Li L, et al. A head-to-head comparison of the efficacy and safety of ixekizumab and adalimumab in biological-naive patients with active psoriatic arthritis: 24-week results of a randomised, open-label, blinded-assessor trial. Ann Rheum Dis. 2020;79(1):123-31.
77. Parisi R, Webb RT, Carr MJ, Moriarty KJ, Kleyn CE, Griffiths CEM, et al. Alcohol-Related Mortality in Patients With Psoriasis: A Population-Based Cohort Study. JAMA Dermatol. 2017;153(12):1256-62.
78. Gupta MA, Schork NJ, Gupta AK, Ellis CN. Alcohol intake and treatment responsiveness of psoriasis: a prospective study. J Am Acad Dermatol. 1993;28(5 Pt 1):730-2.
79. Naldi L. Psoriasis and smoking: links and risks. Psoriasis (Auckl). 2016;6:65-71.
80. Richer V, Roubille C, Fleming P, Starnino T, McCourt C, McFarlane A, et al. Psoriasis and Smoking: A Systematic Literature Review and Meta-Analysis With Qualitative Analysis of Effect of Smoking on Psoriasis Severity. J Cutan Med Surg. 2016;20(3):221-7.

81. Paroutoglou K, Papadavid E, Christodoulatos GS, Dalamaga M. Deciphering the Association Between Psoriasis and Obesity: Current Evidence and Treatment Considerations. Curr Obes Rep. 2020;9(3):165-78.
82. Kokolakis G, Vadstrup K, Hansen JB, Carrascosa JM. Increased Skin Clearance and Quality of Life Improvement with Brodalumab Compared with Ustekinumab in Psoriasis Patients with Aggravating Lifestyle Factors. Dermatol Ther (Heidelb). 2021;11(6):2027-42.
83. Davies H, Bignell GR, Cox C, Stephens P, Edkins S, Clegg S, et al. Mutations of the BRAF gene in human cancer. Nature. 2002;417(6892):949-54.
84. van Jaarsveld CH, ter Borg EJ, Jacobs JW, Schellekens GA, Gmelig-Meyling FH, van Booma-Frankfort C, et al. The prognostic value of the antiperinuclear factor, anti-citrullinated peptide antibodies and rheumatoid factor in early rheumatoid arthritis. Clin Exp Rheumatol. 1999;17(6):689-97.

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8. Eidesstattliche Versicherung

§ 4 Abs. 3. (k) der HabOMed der Charité Hiermit erkläre ich, dass

- weder früher noch gleichzeitig ein Habilitationsverfahren durchgeführt oder angemeldet wurde,

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- mir die geltende Habilitationsordnung bekannt ist.

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