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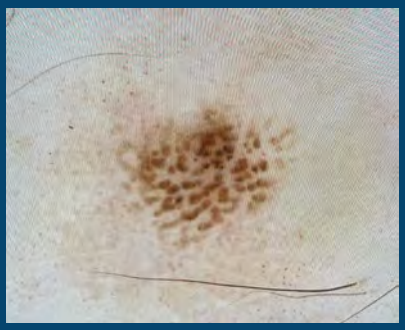

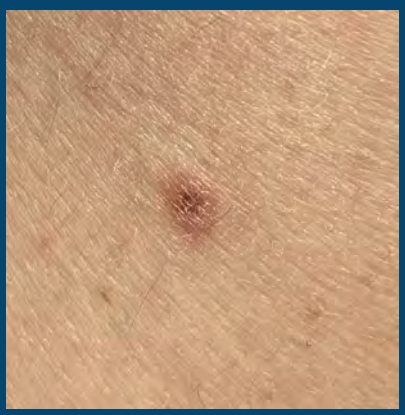

In this issue:

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RESULTADOS CONSISTENTES DE EFICÁCIA E SEGURANÇA DEMONSTRADOS EM DADOS DE VIDA REAL[14-16] MAIS DE 400.000 DOENTES COM DERMATITE ATÓPICA TRATADOS EM TODO O MUNDO[11]

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*moderado a grave em adultos que são candidatos a terapêutica sistémica | **Referências: 1.** RCM - Resumo das características do medicamento. **2.** Gandhi NA et al. Nat Rev Drug Discov 2016; 15:35–500. **3.** Blauvelt A et al. Lancet 2017; 389:2287–2303. **4.** Silverberg JI et al. Acta Derm Venereol 2021; 101(11):adv00585. **5.** Simpson EL et al. JAMA Dermatol 2020; 156(1):44–56. **6.** Data on file (AD-1652 CSR CDLQI rate). Sanofi and Regeneron Pharmaceuticals, Inc. 2019. **7.** Paller AS et al. Am J Clin Dermatol 2020; 21:119–131. **8.** Paller AS et al. J Am Acad Dermatol 2020; 83(5):1282–1293. **9.** Cork MJ et al. Poster presented at the Revolutionizing Atopic Dermatitis Conference; 2021; June 13; Virtual Conference. Poster 468. **10.** Blauvelt A et al. Poster presented at the Revolutionizing Atopic Dermatitis Conference; 2021; June 13; Virtual Conference. Poster 469. **11.** IQVIA Sanofi Integrated DUPIXENT Platform, data through October 2021. **12.** Bagel J et al. Poster presented at the 30th Congress of the European Academy of Dermatology and Venereology; 2021; September 29–October 2; Virtual Meeting. Poster P0257. **13.** de Wijs LEM et al. Br J Dermatol. 2021; 185(3):555–562. **14.** de Wijs LEM et al. Br J Dermatol 2020; 182(2):418–426. **15.** Fargnoli MC et al. J Dermatolog Treat 2021; 32(5):507–513. **16.** Ariëns LF et al. Allergy 2020; 75(1):116–126.

SANOFI – Produtos Farmacêuticos, Lda
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INFORMAÇÕES ESSENCIAIS COMPATÍVEIS COM O RESUMO DAS CARACTERÍSTICAS DO MEDICAMENTO

Nome do medicamento Taltz 80 mg solução injetável em caneta/seringa pré-cheia. **Composição qualitativa e quantitativa** Cada caneta/seringa pré-cheia contém 80 mg de ixecizumab em 1 ml. Ixecizumab é produzido em células de Ovário do Hamster Chinês por tecnologia de ADN recombinante. Lista completa de excipientes, ver "Lista dos excipientes". **Forma farmacêutica** Solução para injeção (injetável). A solução é límpida e incolor a ligeiramente amarelada. **Indicações terapêuticas** Psoríase em placas Taltz é indicado para o tratamento da psoríase em placas, moderada a grave, em adultos que são elegíveis para terapêutica sistémica. Psoríase em placas pediátrica Taltz é indicado para o tratamento da psoríase em placas, moderada a grave, em crianças a partir dos 6 anos de idade e com um peso corporal de, pelo menos, 25 kg, e também em adolescentes elegíveis para terapêutica sistémica. Artrite psoriática Taltz, em monoterapia ou em associação com o metotrexato é indicado para o tratamento da artrite psoriática ativa em doentes adultos com uma resposta insuficiente ou intolerantes ao tratamento com um ou mais fármacos antirreumatismais modificadores da doença (DMARD) (ver secção 5.1 do RCM). Espondiloartrite axial *Espondilite anquilosante (espondiloartrite axial radiográfica)*: Taltz é indicado para o tratamento da espondilite anquilosante ativa em doentes adultos com uma resposta insuficiente à terapêutica convencional. *Espondiloartrite axial não-radiográfica*: Taltz é indicado para o tratamento da espondiloartrite axial não-radiográfica ativa em doentes adultos com sinais objetivos de inflamação, revelados pela elevação da proteína C-reativa (PCR) e/ou imagens de ressonância magnética (RM) e com uma resposta insuficiente a anti-inflamatórios não-esteróides (AINE). **Posologia e modo de administração** Este medicamento deverá ser utilizado sob a orientação e supervisão de um médico com experiência no diagnóstico e tratamento das patologias para as quais é indicado. Posologia *Psoríase em placas em adultos:* A dose recomendada é de 160 mg por injeção subcutânea (duas injeções de 80 mg) na semana 0, seguida de 80 mg (uma injeção) nas semanas 2, 4, 6, 8, 10 e 12, e a partir daí uma dose de manutenção de 80 mg (uma injeção) de 4 em 4 semanas (Q4W). *Psoríase em placas pediátrica (a partir dos 6 anos de idade):* Não estão disponíveis dados de eficácia e segurança em crianças com menos de 6 anos (ver secção 5.1 do RCM). Os dados disponíveis não sustentam a administração em crianças com um peso corporal inferior a 25 kg. A dose recomendada por injeção subcutânea para crianças baseia-se nas seguintes categorias de peso:

Peso corporal da criança	Dose inicial recomendada (semana 0)	Dose recomendada de 4 em 4 semanas (Q4W) daí em diante
Superior a 50 kg	160 mg (duas injeções de 80 mg)	80 mg
25 a 50 kg	80 mg	40 mg

Taltz 80 mg solução injetável em caneta pré-cheia: As doses de ixecizumab de 40 mg devem ser preparadas e administradas por um profissional de saúde qualificado, utilizando a seringa pré-cheia de Taltz 80 mg/1 comercializada. Utilizar a caneta pré-cheia de Taltz 80 mg apenas em crianças que necessitem de uma dose de 80 mg que não precise de ser preparada. Taltz não é recomendado para crianças com um peso corporal inferior a 25 kg. O peso corporal das crianças deve ser registado e revisto periodicamente antes da administração.

Taltz 80 mg solução injetável em seringa pré-cheia: Para crianças às quais seja prescrita a dose de 80 mg, Taltz pode ser administrado usando diretamente a seringa pré-cheia. Consultar as instruções de preparação de Taltz 40 mg na secção 6.6 do RCM. As doses inferiores a 80 mg devem ser preparadas por um profissional de saúde. Taltz não é recomendado para crianças com um peso corporal inferior a 25 kg. O peso corporal das crianças deve ser registado e revisto periodicamente antes da administração.

Artrite psoriática: A dose recomendada é de 160 mg por injeção subcutânea (duas injeções de 80 mg) na semana 0, seguida de 80 mg (uma injeção) de 4 em 4 semanas. Nos doentes com artrite psoriática e, concomitantemente, com psoríase em placas moderada a grave, a posologia recomendada é a mesma da psoríase em placas. *Espondiloartrite axial (radiográfica e não-radiográfica):* A dose recomendada é de 160 mg por injeção subcutânea (duas injeções de 80 mg) na semana 0, seguida de 80 mg de 4 em 4 semanas (ver secção 5.1 do RCM para mais informações). Para todas as indicações (psoríase em placas em adultos e crianças, artrite psoriática e espondiloartrite axial) deve ser considerada a interrupção do tratamento em doentes que não tenham demonstrado resposta após 16 a 20 semanas de tratamento. Alguns doentes que inicialmente apresentam apenas uma resposta parcial podem melhorar posteriormente com a manutenção do tratamento para além das 20 semanas. Populações especiais *Doentes idosos (≥ 65 anos):* Não é necessário ajuste posológico (ver secção 5.2 do RCM). A informação sobre o uso em doentes com idade ≥ 75 anos é limitada. *Compromisso renal ou hepático:* Taltz não foi estudado nestas populações de doentes. Não podem ser feitas recomendações de dose. *População pediátrica Psoríase em placas pediátrica (com um peso corporal inferior a 25 kg e com menos de 6 anos de idade):* Não existe utilização relevante de Taltz em crianças com um peso inferior a 25 kg e com menos de 6 anos para o tratamento da psoríase em placas moderada a grave. *Artrite psoriática pediátrica:* A segurança e a eficácia de Taltz em crianças e adolescentes, entre os 2 e os 18 anos de idade, no tratamento de artrite psoriática (uma categoria da artrite idiopática juvenil) ainda não foram estabelecidas. Não existem dados disponíveis. Não há uso relevante de Taltz em crianças menores de 2 anos para a indicação de artrite psoriática. Modo de administração Uso subcutâneo. A administração de Taltz faz-se por injeção subcutânea. Os locais de injeção podem ser alternados. Se possível, as áreas da pele com psoríase devem ser evitadas como locais de injeção. A solução/caneta/seringa não pode ser agitada. Após treino adequado sobre a técnica de injeção subcutânea, a injeção de Taltz pode ser administrada pelo próprio doente, se o médico considerar apropriado. No entanto, o médico deve assegurar um seguimento apropriado dos doentes. As instruções completas para a administração encontram-se no folheto informativo e no manual do utilizador.*Taltz 80 mg solução injetável em seringa pré-cheia:* As doses inferiores a 80 mg que necessitam de preparação só devem ser administradas por um profissional de saúde. Para instruções acerca da preparação do medicamento antes da administração, ver secção 6.6 do RCM. **Contraindicações** Reações de hipersensibilidade grave à substância ativa ou a qualquer um dos excipientes mencionados na "Lista dos excipientes". Infeções ativas clinicamente relevantes (p. ex. tuberculose ativa, ver "Advertências e precauções especiais de utilização"). **Advertências e precauções especiais de utilização** Rastreabilidade De modo a melhorar a rastreabilidade dos medicamentos biológicos, o nome e o número de lote do medicamento administrado devem ser registados de forma clara. Infeções O tratamento com Taltz está associado a uma taxa acrescida de infeções, tais como infeções do trato respiratório superior, candidíase oral, conjuntivite e tinha (ver "Efeitos indesejáveis"). Taltz deve ser utilizado com precaução em doentes com infeções crónicas clinicamente relevantes ou com história de infeções recorrentes. Os doentes devem ser instruídos a procurar aconselhamento médico, caso se desenvolvam sinais ou sintomas sugestivos de uma infeção. Caso ocorra uma infeção, os doentes devem ser cuidadosamente monitorizados, e a administração de Taltz deve ser interrompida se o doente não responder ao tratamento convencional ou se a infeção se tornar grave. O doente só deve retomar o tratamento com Taltz após a resolução da infeção. Taltz não pode ser administrado a doentes com tuberculose ativa (TB). Deve ser considerada terapêutica antituberculosa antes do início da administração de Taltz em doentes com tuberculose latente. Reações de hipersensibilidade Foram notificadas reações graves de hipersensibilidade, incluindo alguns casos de anafilaxia, angioedema, urticária e, raramente, reações graves de hipersensibilidade retardada (10 a 14 dias após a injeção) incluindo urticária generalizada, dispneia e altos títulos de anticorpos. Caso se verifique uma reação grave de hipersensibilidade, deve suspender-se imediatamente a administração de Taltz e instituir-se uma terapêutica apropriada. Doença inflamatória intestinal (incluindo doença de Crohn e colite ulcerosa) Foram notificados casos de desenvolvimento ou exacerbação de doença inflamatória intestinal com ixecizumab (ver "Efeitos indesejáveis"). O ixecizumab não é recomendado em doentes com doença inflamatória intestinal. Se um doente desenvolver sinais e sintomas de doença inflamatória intestinal ou sentir uma exacerbação de doença inflamatória intestinal pré-existente, o ixecizumab deve ser descontinuado e deve ser iniciado o tratamento médico adequado. Vacinações Taltz não deve ser administrado com vacinas de vírus vivos. Não há dados disponíveis sobre a resposta a vacinas vivas; os dados relativos à resposta a vacinas inativas são insuficientes (ver secção 5.1 do RCM). Excipientes Este medicamento contém menos de 1 mmol de sódio (23 mg) por cada dose de 80 mg, ou seja, é praticamente "isento de sódio". **Interações medicamentosas e outras formas de interação** Nos estudos na psoríase em placas, não foi avaliada a segurança de Taltz em associação com outros agentes imunomoduladores ou fototerapia. Em análises farmacocinéticas da população, a eliminação de ixecizumab não foi afetada pela administração concomitante de corticosteróides orais, AINE, sulfasalazina ou metotrexato. Substratos do citocromo P450 Os resultados de um estudo de interação em doentes com psoríase moderada a grave determinaram que 12 semanas de administração de ixecizumab com substâncias metabolizadas pelo CYP3A4 (i.e. midazolam), CYP2C9 (i.e. varfarina), CYP2C19 (i.e. omeprazol), CYP1A2 (i.e. cafeína) ou CYP2D6 (i.e. dextrometorfano) não tem um impacto clinicamente significativo na farmacocinética dessas substâncias. **Efeitos indesejáveis** Resumo do perfil de segurança As reações adversas mais frequentemente notificadas foram reações no local da injeção (15,5%) e infeções do trato respiratório superior (16,4%) (principalmente nasofaringite). Tabela de reações adversas As reações adversas observadas nos estudos clínicos e nos relatórios pós-comercialização (Tabela 1) estão listadas por classe de sistemas de órgãos segundo o dicionário MedDRA. Dentro de cada classe de sistemas de órgãos, as reações adversas são ordenadas por frequência, começando pelas mais frequentes. Dentro de cada grupo de frequência, as reações adversas são apresentadas por ordem decrescente de gravidade. Além disso, a categoria correspondente para cada frequência de reações adversas é baseada na seguinte convenção: Muito frequentes (≥ 1/10); Frequentes (≥ 1/100 a <1/10); Pouco frequentes (≥ 1/1.000 a <1/100); Raras (≥1/10.000 a <1/1.000); Muito raras (<1/10.000). No total, foram tratados com Taltz 8.956 doentes em estudos clínicos com e sem ocultação na psoríase em placas, artrite psoriática, espondiloartrite axial e outras doenças autoimunes. Destes doentes, 6.385 foram expostos a Taltz durante pelo menos um ano, o que corresponde cumulativamente a uma exposição em adultos de 19.833 doentes-ano e 196 crianças, o quecorresponde cumulativamente a uma exposição de 207 doentes-ano.

Tabela 1. Lista de reações adversas nos estudos clínicos e relatórios pós-comercialização

Classe de sistemas de órgãos	Frequência	Reação adversa
Infeções e infestações	Muito frequentes	Infeção do trato respiratório superior
	Frequentes	Tinha, Herpes simplex (mucocutâneo)
	Pouco frequentes	Gripe, Rinite, Candidíase oral, Conjuntivite, Celulite
Doenças do sangue e do sistema linfático	Pouco frequentes	Neutropenia, Trombocitopenia
Doenças do sistema imunitário	Pouco frequentes	Angioedema
	Raras	Anafilaxia
Doenças respiratórias, torácicas e do mediastino	Frequentes	Dor orofaríngea
Doenças gastrointestinais	Frequentes	Náusea
	Pouco frequentes	Doença inflamatória intestinal
Afeções dos tecidos cutâneos e subcutâneos	Pouco frequentes	Urticária, Erupção cutânea, Eczema
Perturbações gerais e alterações no local de administração	Muito frequentes	Reações no local de injeção[a]

[a] *Ver secção sobre descrição de reações adversas selecionadas.* Descrição de reações adversas selecionadas *Reações no local da injeção:* As reações no local de injeção observadas com maior frequência foram eritema e dor. Estas reações foram predominantemente de gravidade ligeira a moderada e não obrigaram à descontinuação de Taltz. Nos estudos de psoríase em placas em adultos, as reações no local da injeção foram mais frequentes em indivíduos com um peso corporal < 60 kg em comparação com o grupo com um peso corporal ≥ 60 kg (25 % vs. 14 % para o conjunto dos grupos Q2W e Q4W). Nos estudos da artrite psoriática, as reações no local da injeção foram mais frequentes em indivíduos com um peso corporal < 100 kg em comparação com o grupo com um peso corporal ≥ 100 kg (24 % vs. 13 % para o conjunto dos grupos Q2W e Q4W). Nos estudos de espondiloartrite axial, as reações no local da injeção foram semelhantes em doentes com um peso corporal < 100 kg comparativamente ao grupo com um peso corporal ≥ 100 kg (14 % vs. 9 % para o conjunto dos grupos Q2W e Q4W). O aumento da frequência das reações no local da injeção no conjunto dos grupos Q2W e Q4W não levou a um aumento das descontinuações em nenhum dos estudos de psoríase em placas, artrite psoriática ou espondiloartrite axial. Os resultados descritos acima foram obtidos com a formulação original de Taltz. Num estudo mono-ocultado, cruzado e aleatorizado em 45 indivíduos saudáveis, ao se comparar a formulação original com a formulação revista, sem citrato, foram obtidas pontuações de dor EVA significativamente mais baixos estatisticamente com a formulação sem citrato versus a formulação original, durante a injeção (diferença LSM na pontuação EVA -21,69) e 10 min após a injeção (diferença LSM na pontuação EVA -4,47). *Infeções:* Nos ensaios clínicos de fase III controlados por placebo, na psoríase em placas em adultos, foram notificadas infeções em 27,2% dos doentes tratados com Taltz por um período máximo de 12 semanas em comparação com 22,9% dos doentes tratados com placebo. Na sua maioria, as infeções foram não graves e ligeiras a moderadas, não tendo sido necessário interromper o tratamento na maioria dos casos. Ocorreram infeções graves em 13 (0,6%) dos doentes tratados com Taltz e em 3 (0,4%) dos doentes tratados com placebo (ver "Advertências e precauções especiais de utilização"). Durante todo o período de tratamento, foram notificadas infeções em 52,8% dos doentes tratados com Taltz (46,9 por 100 doentes-ano). Foram reportadas infeções graves em 1,6% dos doentes tratados com Taltz (1,5 por 100 doentes-ano). As taxas de infeção observadas nos estudos clínicos na artrite psoriática e na espondiloartrite axial foram semelhantes às observadas nos estudos na psoríase em placas, com exceção da frequência das reações adversas de gripe e conjuntivite, que foram frequentes em doentes com artrite psoriática. *Avaliação laboratorial de neutropenia e trombocitopenia:* Nos estudos na psoríase em placas, 9% dos doentes tratados com Taltz desenvolveram neutropenia. Na maioria dos casos, a contagem de neutrófilos foi ≥ 1.000 células/mm^3. Estes níveis de neutropenia podem persistir, flutuar ou ser transitórios. 0,1% dos doentes tratados com Taltz apresentaram uma contagem de neutrófilos <1.000 células/mm^3. Em geral, a neutropenia não obrigou à interrupção de Taltz. 3% dos doentes tratados com Taltz, passaram de uma contagem normal de plaquetas, no início do estudo, para <150.000 plaquetas/mm^3 a ≥75.000 plaquetas/mm^3. A trombocitopenia pode persistir, flutuar ou ser transitória. A frequência de neutropenia e trombocitopenia nos estudos clínicos na artrite psoriática e na espondiloartrite axial é semelhante à observada nos estudos na psoríase em placas. *Imunogenicidade:* Aproximadamente 9 a 17% dos doentes adultos com psoríase em placas tratados com Taltz, de acordo com o regime posológico recomendado, desenvolveram anticorpos antifármaco, na sua maioria de baixo título e não associados a uma diminuição da resposta clínica até às 60 semanas de tratamento. No entanto, aproximadamente 1% dos doentes tratados com Taltz apresentaram anticorpos neutralizantes associados a baixas concentrações do fármaco e a uma redução da resposta clínica. Em doentes com artrite psoriática tratados com Taltz de acordo com o regime posológico recomendado até 52 semanas, aproximadamente 11% desenvolveram anticorpos antifármaco, na sua maioria de baixo título, e aproximadamente 8% apresentaram anticorpos neutralizantes. Não se observou qualquer associação aparente entre a presença de anticorpos neutralizantes e o impacto nas concentrações do fármaco ou na sua eficácia. Em doentes com psoríase pediátrica tratados com Taltz de acordo com o regime posológico recomendado até às 12 semanas, 21 doentes (18%) desenvolveram anticorpos antifármaco, aproximadamente metade de baixo título e 5 doentes (4%) apresentaram anticorpos neutralizantes confirmados associados às baixas concentrações do fármaco. Não se observou qualquer associação com a resposta clínica ou com acontecimentos adversos. Em doentes com espondiloartrite axial radiográfica tratados com Taltz com o regime posológico recomendado por um período de até 16 semanas, 5,2% desenvolveram anticorpos antifármaco, na sua maioria de baixo título, e 1,5% (3 doentes) apresentaram anticorpos neutralizantes (NAb). Nestes 3 doentes, as amostras NAb-positivas tinham baixas concentrações de ixecizumab, e nenhum destes doentes atingiu uma resposta ASAS40. Em doentes com espondiloartrite axial não-radiográfica tratados com Taltz com o regime posológico recomendado por um período de até 52 semanas, 8,9% desenvolveram anticorpos antifármaco, todos eles de baixo título; nenhum doente apresentou anticorpos neutralizantes; e não se observou qualquer associação aparente entre a presença de anticorpos antifármaco e a concentração do fármaco, a sua eficácia ou segurança. Para todas as indicações, não ficou claramente estabelecida a existência de uma associação entre imunogenicidade e acontecimentos adversos decorrentes do tratamento. População pediátrica O perfil de segurança observado em crianças com psoríase em placas tratados com Taltz de 4 em 4 semanas é consistente com o perfil de segurança em doentes adultos com psoríase em placas, à exceção da frequência de conjuntivite, gripe e urticária, que foram frequentes. A doença inflamatória intestinal também foi mais frequente em doentes pediátricos, embora tenha sido pouco frequente. No estudo clínico pediátrico, verificou-se a ocorrência de doença de Crohn em 0,9% dos doentes do grupo de tratamento com Taltz e 0% dos doentes do grupo placebo durante o período de 12 semanas, controlado com placebo. Verificou-se a ocorrência de doença de Crohn num total de 4 doentes tratados com Taltz (2,0%) durante o período controlado com placebo e de manutenção combinado, no estudo clínico pediátrico. Notificação de suspeitas de reações adversas A notificação de suspeitas de reações adversas após a autorização do medicamento é importante. Ela permite uma monitorização contínua da relação benefício/risco do medicamento. Pede-se aos profissionais de saúde que notifiquem quaisquer suspeitas de reações adversas através do: Sítio da internet: http://www.infarmed.pt/web/infarmed/submissaoram (preferencialmente) ou através dos seguintes contactos: Direção de Gestão do Risco de Medicamentos, Parque da Saúde de Lisboa, Av. Brasil 53. 1749-004 Lisboa. Tel: +351 21 798 73 73. Linha do Medicamento: 800222444 (gratuita). E-mail: farmacovigilancia@infarmed.pt **Data de revisão do texto** 16 de dezembro de 2021. Está disponível informação pormenorizada sobre este medicamento no sítio da internet da Agência Europeia de Medicamentos: http://www.ema.europa.eu/. Medicamento sujeito a receita medica restrita. Para mais informações devera contatar o representante local do Titular da Autorização de Introdução no Mercado.

Referências: 1. RCM Taltz®.

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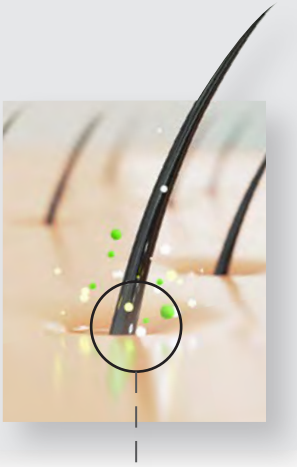
Cover design: Histopathology of the skin biopsy with a dermal granulomatous reaction, predominantly superficial, with periadnexal and perivascular involvement (H&E ×40). See article by Freitas et al. in this issue.

minox®5

Minoxidil 50 mg/ml

ALOPECIA ANDROGENÉTICA



SERÃO TODAS IGUAIS AS FORMULAÇÕES DE MINOXIDIL 5% ?

O Minoxidil é um pró-fármaco. É convertido na sua forma ativa, sulfato de minoxidil pela enzima sulfotransferase (principalmente pela sua forma SULT1A1) localizada na bainha externa da raíz do folículo piloso.[1]

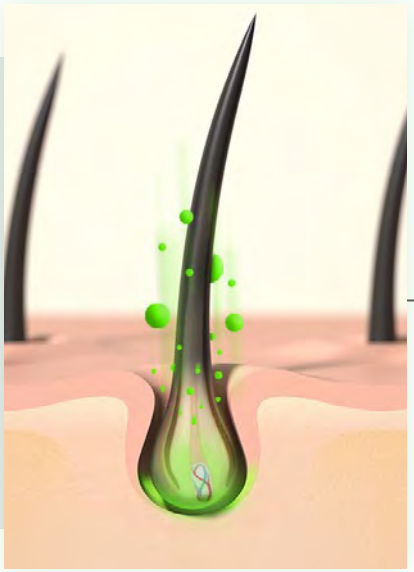
PORQUE É QUE A INCLUSÃO DE PROMOTORES DE PERMEAÇÃO É TÃO IMPORTANTE?

PORQUE O VEÍCULO IMPORTA

O MINOX 5 CONTÉM ÁCIDO SALICÍLICO, ÁLCOOL ISOPROPÍLICO E ETANOL.

O ácido salicílico tópico, até à concentração de 3%, possui um efeito queratoplástico.[2]
Está presente na formulação de minox 50 mg/ml.

ETANOL	ALCOOL ISOPROPÍLICO	PROPILENOGLICOL
C_2H_6O [5]	C_3H_8O [5]	$C_3H_8O_2$ [5]



PROPILENOGLICOL

Habitualmente uma concentração entre 1% - 10% em testes de irritação cutânea é a recomendada para evitar irritação cutânea. [4]

O PG é usado desde 1932 como promotor de permeação de fármacos na pele em preparações tópicas. [3]

A APLICAÇÃO LOCALIZADA FAVORECE A AÇÃO DO VEÍCULO

Minox® 5 é um MNSRM | NC
Laboratório Edol - Produtos Farmacêuticos, S. A. Av. 25 de Abril, n.º 6-6A 2795-225 Linda-a-Velha | Contrib. Nº 507072642 | Portugal | DMK MIN 09/22 Out 23

Referências:

(1) Dhurat R, Daruwalla S, Pai S, et al., SULT1A1 (Minoxidil Sulfotransferase) enzyme booster significantly improves response to topical minoxidil for hair regrowth. J Cosmet Dermatol. 2021;00:1–4
(2) Fonseca M., Oliveira S. P., Lubi N. C., "OS BENEFÍCIOS DO PEELIG DE ÁCIDO SALICÍLICO NA ACNE VULGAR", consultado em 24/10/2022, https://docplayer.com.br/47825092-Os-beneficios-do-peelig-de-acido-salicilico-na-acne-vulgar.html
(3) Majella E. Lane, Skin penetration enhancers, Int J Pharmaceutics, 2013, 447(1–2) , pp 12-21
(4) Funk J., Maibach H., Propylene glycol dermatitis: re-evaluation of an old problem, Contact dermatitis, 1994, 31, 236-241
(5) https://go.drugbank.com/drugs/ Consultado em 23/12/2022

INFORMAÇÕES ESSENCIAIS COMPATÍVEIS COM O RESUMO DAS CARACTERÍSTICAS DO MEDICAMENTO | **NOME DO MEDICAMENTO** minox 5, 50 mg/ml, Solução cutânea. | **COMPOSIÇÃO QUALITATIVA E QUANTITATIVA** Cada mililitro de solução cutânea contém 50 mg de minoxidil. Excipiente(s) com efeito conhecido: Etanol a 96% - 245,9 mg/ml. Propilenoglicol - 100 mg/ml. Lista completa de excipientes: álcool isopropílico, propilenoglicol, ácido salicílico, etanol a 96%, água para preparações injetáveis. | **FORMA FARMACÊUTICA** Solução cutânea. Solução límpida, incolor a ligeiramente amarelada, com odor característico a álcool. | **INDICAÇÕES TERAPÊUTICAS** Tratamento da calvície masculina e feminina, designada por alopecia androgenética. Tratamento da alopecia areata, vulgarmente conhecida por pelada. | **POSOLOGIA E MODO DE ADMINISTRAÇÃO** Minox 5 destina-se apenas a uso externo, para aplicação no couro cabeludo, duas vezes por dia (12/12h), no cabelo completamente seco. A dose por cada aplicação é de 1 ml de solução (corresponde a 30 gotas), qualquer que seja a área a tratar, espalhando o medicamento do centro para a periferia com os dedos. A dose diária recomendada é de 2 ml e não deve ser excedida pois corre o risco de provocar efeitos sistémicos. No caso de omitir uma dose, continue as aplicações normalmente sem duplicar a dose. O tratamento dura cerca de um ano, período ao fim do qual se observam os melhores resultados. A utilização de minoxidil a 5% deverá ser interrompida se ao fim de 4 meses de utilização não se verificar crescimento capilar. Para continuar a obter melhoria e manter os benefícios conseguidos, as aplicações deverão ser mantidas duas vezes por dia após a fase de ataque que pode durar cerca de 6 meses. A terapêutica poderá ser iniciada com Minox 5, conforme critério e avaliação clínica da alopecia. A interrupção do tratamento poderá induzir um retorno ao estado de alopecia inicial ao fim de 3 a 4 meses. A experiência tem demonstrado que os resultados são tanto melhores quanto mais precoce é o início do tratamento, circunstância em que há maior número de folículos pilosos em condições de responder ao efeito do medicamento. Por outro lado, o estado do cabelo, a duração da alopecia e a área a tratar também parecem ter um papel relevante na obtenção de resultados cosmeticamente aceitáveis. População pediátrica Minox 5 não se destina para utilização em crianças. | **CONTRAINDICAÇÕES** Minox 5 está contraindicado em: - Hipersensibilidade à substância ativa ou a qualquer um dos excipientes mencionados na secção "Composição qualitativa e quantitativa". - Doentes com hipertensão arterial ou doença cardiovascular, nomeadamente insuficiência coronária (possíveis efeitos sistémicos se ocorrer absorção significativa). - Indivíduos com psoríase do escalpo, dermatite seborreica, queimadura solar, irritação ou abrasão no couro cabeludo. - Gravidez e aleitamento (ver secção 4.6 e 5.3 do RCM). População pediátrica Não é indicada a utilização de Minox 5 em crianças e indivíduos com menos de 18 anos. | **ADVERTÊNCIAS E PRECAUÇÕES ESPECIAIS DE UTILIZAÇÃO** Sempre que se observe reação, no local de aplicação, nomeadamente irritação ou prurido, foliculites ou descamação deve ser consultado um dermatologista. No caso de reação grave deve ser imediatamente lavado o couro cabeludo e não voltar a aplicar sem contactar previamente o médico. Caso o Minox 5 atinja acidentalmente zonas sensíveis (olhos) estas devem ser lavadas imediatamente com água fria corrente e abundante. Se a irritação persistir deve consultar-se o médico. Devido ao facto do tratamento com minoxidil poder provocar retenção de líquidos, recomenda-se precaução em doentes com história de insuficiência cardíaca, disfunção ventricular ou hipertensão e em doentes com edema pré-existente devido a outra etiologia. A utilização da solução cutânea de minoxidil deve ser interrompida, até contactar o médico, se ocorrerem palpitações, dores no peito, tonturas ou cefaleias. Deve manter-se vigilância clínica apropriada nos doentes idosos e nos doentes com disfunção renal, hepática ou cardíaca, que estejam a aplicar minoxidil. Sintomas isquémicos podem ser agravados pelo uso de minoxidil em indivíduos com doença coronária arterial. Nos estudos clínicos, os efeitos sistémicos cardiovasculares, durante o tratamento com minoxidil tópico vs placebo (6 meses), foram avaliados e a pressão arterial não sofreu alterações, no entanto houve aumento da frequência cardíaca e débito cardíaco. Foi relatado em alguns estudos clínicos, de longa duração, que algumas mulheres desenvolveram hipertricose difusa. Esta deverá ser avaliada para confirmar a sua persistência. A terapêutica deverá ser interrompida se forem detetados resultados anormais persistentes. Os riscos de sintomas sistémicos estão aumentados com a frequência das doses, desta forma a aplicação de doses para além do recomendado pode originar sintomas sistémicos. O uso de minoxidil tópico não é recomendado em mulheres que pretendam engravidar porque existe risco de hipertricose no recém-nascido. O aumento da queda de cabelo pode ocorrer devido à ação do minoxidil, que provoca a alteração da fase telogénica de repouso para a fase anagénica de crescimento (o cabelo velho cai enquanto o novo vai ocupar o seu lugar). Este aumento temporário de queda de cabelo ocorre geralmente 2 a 8 semanas após o início do tratamento e desaparece após algumas semanas (primeiro sinal de ação de minoxidil). Se a queda de cabelo persistir, o utilizador deve suspender a utilização de Minox 5 e consultar um médico. Este medicamento contém 100 mg de propilenoglicol em cada ml. Este medicamento contém 245,9 mg de etanol a 96% em cada ml e como tal é inflamável e não deverá ser utilizado junto a fontes de calor ou chama. Pode causar sensação de queimadura na pele lesionada. | **INTERAÇÕES MEDICAMENTOSAS E OUTRAS FORMAS DE INTERAÇÃO** Interações farmacodinâmicas: A aplicação concomitante de minoxidil e corticoides tópicos pode aumentar o efeito do minoxidil. A vaselina, pelo seu efeito oclusivo, pode aumentar a absorção do minoxidil. Retinoides tópicos nomeadamente tretinoína e isotretinoína aumentam a absorção cutânea devido ao aumento da permeabilidade do estrato córneo. A absorção percutânea do minoxidil é tripla quando aplicada juntamente com tretinoína, o que pode originar um efeito sinergético. No entanto, a segurança e a eficácia da terapia combinada de minoxidil e retinoides requer um estudo mais aprofundado. A administração de minoxidil tópico e antralina, com propriedades irritantes, origina um efeito sinergético que pode ser útil no tratamento de alopecia areata extensa e resistente. Minoxidil sistémico pode aumentar o risco de toxicidade do minoxidil tópico se forem usados ao mesmo tempo, sendo que indivíduos tratados com terapêutica concomitante devem ser monitorizados. **Interações farmacocinéticas:** ***- O efeito do minoxidil na farmacocinética de outros fármacos:*** Em estudos sobre interações medicamentosas, o minoxidil tópico não parece ter efeitos clinicamente importantes na farmacocinética de outros fármacos. No entanto, tendo em conta a possibilidade de absorção sistémica, pode ocorrer potenciação da hipotensão ortostática em pacientes sob terapêutica por guanetidina e betanidina. ***- O efeito de outros fármacos na farmacocinética do minoxidil:*** A farmacocinética do minoxidil tópico, dada a sua baixa absorção, não parece ser afetada de forma clinicamente relevante por outros fármacos, no entanto a presença de antralina pode favorecer a absorção sistémica de minoxidil, tendo em conta que altera a permeabilidade da pele devido às suas propriedades irritativas. | **EFEITOS INDESEJÁVEIS** A informação abaixo lista as reações adversas por classes de sistemas de órgãos e frequência. Em cada grupo de frequência, as reações adversas são apresentadas por ordem decrescente de gravidade. As frequências são definidas como: muito frequentes (≥1/10), frequentes (≥1/100, <1/10), pouco frequentes (≥1/1000, <1/100), raros (≥1/10 000, <1/1000), muito raros (<1/10000), desconhecido (não pode ser calculado a partir dos dados disponíveis). Os seguintes efeitos indesejáveis relacionados com o fármaco minoxidil foram reportados: Doenças do sistema imunitário: Desconhecido: Reações alérgicas, incluindo angioedema. Perturbações do foro psiquiátrico: Raros: Delírio, ansiedade. Doenças do sistema nervoso: Raros: Cefaleias, tonturas, vertigens. Afeções oculares: Raros: Perturbações visuais (diminuição acuidade visual), conjuntivites. Afeções do ouvido e do labirinto: Raros: Sensação de zumbidos, otite externa. Cardiopatias: Pouco frequentes: Palpitações, dores no peito (angina), taquicardia, alteração do eletrocardiograma (ECG); aumento da frequência cardíaca; aumento do débito cardíaco. (Nota: não foi estabelecida relação causal ao nível dos efeitos cardiovasculares e a aplicação tópica de minoxidil) Afeções dos tecidos cutâneos e subcutâneos: Frequentes (as reações adversas mais frequentemente observadas nos estudos clínicos foram reações dermatológicas minor): Prurido, secura, descamação, irritação e dermatite irritativa, sensação de queimadura, hipertricose difusa reversível (face, sobrancelha, ouvido, braços). Pouco frequentes: Eczema, foliculite, eritema local, exacerbação da dermatite seborreica, dermatite alérgica de contacto. Raros: Alopecia, alterações capilares. Desconhecido: Aumento da queda de cabelo no início do tratamento (ver secção "Advertências e precauções especiais de utilização"). Doenças renais e urinárias: Raros: Infeções urinárias, cálculo enal. Doenças dos órgãos genitais e da mama: Raros: Disfunção sexual. Perturbações gerais e alterações no local de administração: Pouco frequentes: Edema (retenção de líquidos e de sal). Raros: Fraqueza, astenia. (Nota: não foi estabelecida relação causal ao nível dos efeitos no sistema nervoso, aparelho reprodutor, urinário e olhos e a aplicação tópica de minoxidil). Sinais e sintomas de absorção sistémica: Dores no peito (angina), batimento cardíaco irregular e acelerado, hipotensão, nevrite, edema, vasodilatação. Na eventualidade de ocorrerem efeitos colaterais sistémicos, aconselha-se a suspensão do fármaco. **Notificação de suspeitas de reações adversas:** A notificação de suspeitas de reações adversas após a autorização do medicamento é importante, uma vez que permite uma monitorização contínua da relação benefício-risco do medicamento. Pede-se aos profissionais de saúde que notifiquem quaisquer suspeitas de reações adversas diretamente ao INFARMED, I. P.: Sítio da internet: http://www.infarmed.pt/web/infarmed/submissaoram (preferencialmente) ou através dos seguintes contactos: Direção de Gestão do Risco de Medicamentos, Parque da Saúde de Lisboa, Av. Brasil 53, 1749-004 Lisboa, Tel: +351 21 798 73 73, Linha do Medicamento: 800222444 (gratuita), E-mail: farmacovigilancia@infarmed.pt. **(v.12.2019) Para mais informações deverá contactar o titular da autorização de introdução no mercado: Laboratório Edol – Produtos Farmacêuticos, S.A.** | Av. 25 de Abril, 6-6A, 2795-225 Linda-a-Velha, Portugal

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CUIDADOS PARA **PELE OLEOSA COM TENDÊNCIA ACNEICA**

EFICÁCIA CLINICAMENTE DEMONSTRADA
EFEITO ANTI-RECIDIVA
28 DIAS

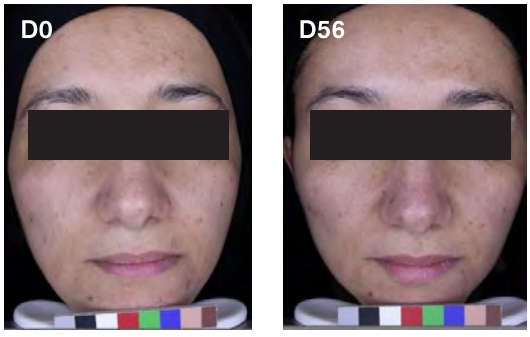
LIGEIRO[3] **MODERADO[3]** **SEVERO[4]**

RESULTADOS

+150%
AFINA O GRÃO DA PELE[1]

+130%
TEZ MAIS UNIFORME[1]

-35%
COMEDÕES E MICROQUISTOS[2]



Estudo clínico comparativo sob controlo dermatológico em 52 indivíduos com acne - resultados no grupo Hyséac Sérum após 56 dias de aplicação duas vezes por dia.
1. Pontuação clínica pelo dermatologista.
2. Contagem de lesões pelo dermatologista.
3. Sozinho, em combinação ou após terapêuticas medicamentosas.
4. Hidrata e acalma a pele fragilizada por tratamentos deslipidantes.

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PODE UMA ROTINA COM CERAMIDAS MELHORAR CLINICAMENTE A XEROSE E A QUALIDADE DE VIDA EM DOENTES IDOSOS COM MEDICAÇÃO CONCOMITANTE?

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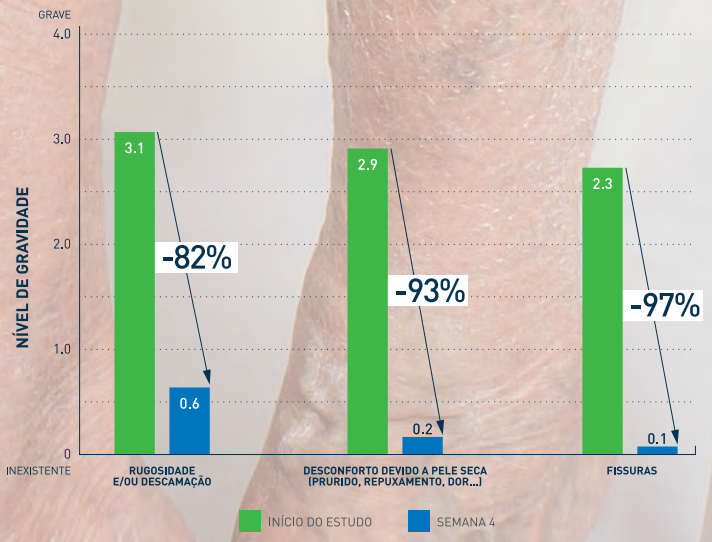
ESTUDO NOVO CLÍNICO

AVALIAÇÃO DERMATOLÓGICA

Até **97% de MELHORIA** dos sinais e sintomas de pele seca em apenas 4 semanas



*Hydrating Cleanser + Moisturising Cream

Protocolo: Foi realizado um estudo clínico de 4 semanas, num único centro, em 30 mulheres e homens com mais de 70 anos, com evidências de xerose e/ou descamação, com uma doença sistémica e/ou sob medicação concomitante com o efeito secundário de xerose. Hydrating Cleanser foi utilizado pelo menos uma vez por dia no corpo e Moisturising Cream foi aplicado duas vezes por dia no corpo. A eficácia foi avaliada por classificação clínica no início do estudo e na semana 4. Foram tiradas fotografias e realizadas auto-avaliações no início do estudo e na semana 4.

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EFFACLAR H ISO-BIOME

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Apazigua e hidrata a barreira cutânea e atua no microbioma

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REEQUILIBRA O MICROBIOMA

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ACALMA E REDUZ A INFLAMAÇÃO

VITAMINA B5*
GLICERINA E ESQUALANO
REPARA E HIDRATA

PROCERAD*
REDUZ AS MARCAS

0.25% EXTRATO DE ORELLANA*
REDUZ A HIPERQUERATINIZAÇÃO E REGULA A PRODUÇÃO DE SEBO
REDUZ A VIRULÊNCIA DA C.ACNES

*NOVO INGREDIENTE

91% **REFERE QUE SENTE A PELE CONFORTÁVEL[1]**

98% **REFERE QUE A APLICAÇÃO É FÁCIL E CALMANTE[1]**

-66% **SECURA[2]**

-71% **DESCAMAÇÃO[2]**

-27% **ERITEMA[2]**

1. 55 indivíduos com pele seca na face sob tratamento com Isotretinoína (Roaccutane). Aplicação do produto na face duas vezes ao dia durante 4 semanas.
2. Estudo clínico sob controlo dermatológico com 44 indivíduos em tratamento EPIDUO com rotina cosmética não eficaz no controlo da sensibilidade da pele durante mais de 1 mês; estudo durante 28 dias. Avaliação da QoL pelo dermatologista

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EDITORIAL

Thriving for indexation of the Portuguese Journal of Dermatology and Venereology

No caminho para a indexação do Portuguese Journal of Dermatology and Venereology

Margarida Gonçalo[1,2,a]* *and Tiago Torres*[3,4,b]

[1]Dermatology Department, Centro Hospitalar e Universitário de Coimbra, Coimbra; [2]Dermatology Service, Faculty of Medicine, Universidade de Coimbra, Coimbra; [3]Dermatology Service, Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto, Porto; [4]Dermatology Department, Centro Hospitalar Universitário do Porto, Porto, Portugal

[a]*ORCID: 0000-0001-6842-1360;* [b]*ORCID: 0000-0003-0404-0870*

After one year of publication of the Portuguese Journal of Dermatology and Venereology by the new publisher, Permanyer, the official Journal of the Portuguese Society of Dermatology and Venereology is on track to obtain the credits that will allow us to apply for indexation in PubMed/PubMed Central. We are already indexed in the Directory of Open Access Journals, Scielo, Google Scholar, and the Index das Revistas Médicas Portuguesas, but there is still a long way to go to PubMed.

We need the collaboration of all the Portuguese dermatologists, as this is our journal that we have to appreciate and feel as ours. It is open to and enriched by manuscripts from all over the world (we actually have been publishing manuscripts from many foreign countries), but we count on the national contributions of all of us.

Our Portuguese Dermatology, which is so rich, needs to have an expression in our own journal. We have so many young and "less young" colleagues that are so highly recognized in Portugal and abroad and are giving such an important contribution to dermatology, with their basic and clinical investigation, with international multicenter collaborations, publishing individually or within international groups in highly rated journals, that we hope they can really improve our Journal and help it go into the next step. There is still some lack of organization among all of us, but we foresee much more collaboration among the younger generation that will certainly enrich our dermatology and our journal.

We take this opportunity to thank all those who have collaborated with us, authors, reviewers, associate editors, and readers, but we need to involve you more, both with new original manuscripts and with the revisions that are essential to improve the quality of the published manuscripts.

Let's begin this New Year aiming to reach our highest standards and achieve one of our main goals— indexation in PubMed!

***Corresponding author:**
Margarida Gonçalo
E-mail: mmgoncalo@gmail.com

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ORIGINAL ARTICLE

Epidemiological profile between 2020-2021 of patients with lichen planus treated in a tertiary hospital

Perfil epidemiológico entre 2020-2021 de pacientes com líquen plano tratados em hospital terciário

Fernanda Del Rio[a], Thayane Lemos, Felipe Tavares, Manuela Cabral, and Ana L. Sampaio*

Department of Dermatology, Pedro Ernesto University Hospital, Universidade do Estado do Rio de Janeiro, Rio de Janeiro, Brazil
[a]ORCID: 0000-0003-4446-634X

Abstract

Background: Lichen planus (LP) is a chronic inflammatory dermatosis of unknown etiology that manifests in various clinical forms on the skin, oral and genital mucosa, scalp, and nails. Reports have suggested that anxiety, stress, diabetes, autoimmune diseases, drugs and genetic predisposition may be triggers of the disease. Meanwhile, the association of LP with hepatitis C virus infection remains controversial. **Objectives:** To analyze the epidemiological profile of patients treated in a tertiary hospital and compare our findings with those in the literature. **Methods:** We conducted a retrospective cross-sectional observational study of patients with lesions of histopathologically confirmed LP who were treated in a tertiary hospital from January 2020 to January 2021. Additionally, we analyzed the association of LP with comorbidities, including hepatitis C and smoking. **Results:** Overall, 24 patients were included in the study. Of these, 19 (79%) were women, and 13 (55%) had comorbidities, including hypertension and diabetes mellitus. Additionally, 29% of the patients were smokers. The most common forms of LP found were cutaneous (15 patients, 63%), followed by a cutaneous plus nail (four patients, 17%), cutaneous plus oral (three patients, 12%) and nail (two patients, 8%) forms. Moreover, 20/24 (83%) patients with documented serology for hepatitis C showed negative results; however, one of these patients was treated for HCV 5 years before the onset of LP. **Conclusions:** The present study demonstrated that LP is more prevalent in women and those with higher phototypes (Fitzpatrick > III). In addition, it has several associated comorbidities. Meanwhile, although the association of LP with hepatitis C has been reported, we did not observe this in our study. Future studies with larger sample sizes should be conducted to confirm our results.

Keywords: Cutaneous lichen planus. Hepatitis C. Lichen planus. Mucous lichen planus. Research article.

Resumo

Fundamentos: Líquen Plano (LP) é uma dermatose inflamatória crônica de etiologia desconhecida, que se manifesta de várias formas clínicas na pele, mucosa oral e genital, couro cabeludo e unhas. Relatos sugerem que ansiedade, diabetes, doenças autoimunes, drogas, estresse e predisposição genética podem ser gatilhos da doença. Enquanto isso, a associação do LP com a infecção pelo vírus da hepatite C permanece controversa. **Objetivos:** Analisar o perfil epidemiológico dos

***Corresponding author:**
Fernanda Del Rio
E-mail: fedelrio@hotmail.com

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doentes observados em num hospital terciário e comparar os nossos achados com os da literatura. **Métodos:** Realizou-se um estudo observacional transversal retrospectivo de doentes com lesões de LP histopatológico confirmados que foram tratados em um hospital terciário de janeiro de 2020 a janeiro de 2021. Além disso, analisamos a associação do LP com comorbilidades, incluindo hepatite C e o tabagismo. **Resultados:** Ao todo, 24 doentes foram incluídos no estudo. Destes, 19 (79%) eram mulheres e 13 (55%) tinham comorbilidades, como, por exemplo, hipertensão e diabetes. Além disso, 29% dos doentes eram fumantes ativos. As formas mais comuns de LP encontradas foram formas cutâneas (15 doentes, 63%), seguidas pela cutânea associada ao acometimento ungueal (4 doentes, 17%), cutânea associada ao acomentimento oral (3 doentes, 12%) e ungueal (2 doentes, 8%). Além disso, 20/24 (83%) doentes apresentaram dosagem serologia documentada para hepatite C; destes, um caso positivo foi tratado 5 anos antes do início do LP. **Conclusões:** O presente estudo demonstrou que o LP é mais prevalente em mulheres e aqueles com fototipos mais elevados (Fitzpatrick > III). Além disso, apresenta diversas comorbilidades associadas. Embora tenha sido relatada associação de LP com hepatite C, não observamos isso no nosso estudo. Estudos futuros com tamanhos amostrais maiores dimensões devem ser realizados de modo a confirmar nossos resultados.

Palavras-chave: Líquen plano. Líquen plano cutâneo. Líquen plano mucoso. Hepatite C.

Introduction

Lichen planus (LP) is a chronic, autoimmune, and inflammatory condition that affects the skin and is mediated by T cells. Notably, it is more prevalent in middle-aged women[1,2]. The etiology of the disease remains unknown, but possible trigger factors have been identified, including anxiety, diabetes, autoimmune diseases, drugs, stress and genetic predisposition. LP can affect several parts of the body, such as the skin, nails, and oral, vulvovaginal, esophageal, laryngeal, and conjunctival mucous membranes. LP has different subtypes that can be characterized depending on the site of involvement and morphology of the lesion. Most cases manifest with violaceous papules or plaques, which can be very pruritic and can be covered by white striations (Wickham striae)[3,4]. The disease affects < 1% of the world's adult population; however, the oral form, which is the most prevalent, is present in up to 4% of adults[5]. Currently, epidemiological studies regarding LP are few and do not reflect the situation in Brazil.

Several studies have reported a relationship between hepatitis C virus infection and LP, and they have suggested that hepatitis C could be an etiological agent of LP[6]. However, the causal relationship between the two diseases has not been established; if they are related, it is unknown whether LP lesions are triggered directly by the virus or through an immunological reaction. Meanwhile, a higher prevalence of the oral LP subtype has been described in patients with positive hepatitis C serology. Nevertheless, data regarding the relationship between hepatitis C and LP remain controversial and vary depending on the country and prevalence of hepatitis C[7,8].

Objectives

This study assessed the epidemiological profile of patients with LP treated in a tertiary hospital and compared the findings with those in the literature.

Materials and methods

We conducted a retrospective cross-sectional observational study that evaluated the electronic medical records of patients with histopathologically confirmed LP who presented to the dermatology service from January 2020 to January 2021. Histopathological findings of LP included orthokeratic hyperkeratosis, wedge hypergranulosis, irregular acanthosis in sawtooth arrangement, dermoepidermal band-like inflammatory infiltrate, and liquefaction degeneration of the basal layer[9]. Additionally, patient data, including comorbidities, smoking, and hepatitis C serology, were obtained from the medical records, if available. Patients without histopathological confirmation of LP were excluded from the study.

Results

A total of 24 patients were included in the study. The mean age of the participants was 53.6 years, 16 (66.6%) patients were Fitzpatrick phototype IV/V, and 19 (79%) were women. Of the 24 patients, 13 (55%) had comorbidities. Among the most prevalent comorbidities were hypertension (10 patients, 42%), diabetes mellitus (six patients, 25%), hyperthyroidism (one patient, 4%), dyslipidemia (two patients, 8%), and depressive disorder (three patients, 13%), and seven patients reported smoking habits (29%), Overall, 22 (92%) patients had cutaneous lesions, six (25%) had nail lesions, and three

Table 1. Epidemiological profile of the 24 patients with lichen planus

Variables	Number (n = 24)	%
Age		
< 20	1	4%
20-40	2	8%
40-60	11	46%
> 60	10	42%
Phototype		
I or II	8	33.33%
III or IV	8	33.33%
V or VI	8	33.33%
Gender		
Men	5	21%
Women	19	79%
Comorbidities		
Yes	13	55%
No	11	45%
Related comorbidities		
Hyperthyroidism	1	4%
Diabetes *mellitus* type 2	4	17%
Diabetes insulin-dependent	2	8%
Prediabetes	2	8%
Dyslipidemia	2	8%
Depression	3	13%
Hypertension	10	42%
Patients with more than one comorbidity	8	62%
Smoking		
Yes	7	29%
No	17	71%
Sub-type of LP		
Cutaneous	15	63%
Cutaneous + nail	4	17%
Cutaneous + oral	3	12%
Nail	2	8%
Types of cutaneous LP (n = 15)		
Classical LP	9	60%
Pigmented LP	2	13%
Hypertrophic LP	1	7%
Inverted LP	1	7%
Overlap between lupus erythematosus and LP	2	13%
HCV serology (n = 20)		
HCV positive	0	0%
HCV negative	20	100%

(12%) had oral mucosal lesions. Meanwhile, 15 (63%) had cutaneous LP, nine (60%) had classical LP, two (13%) had pigmented LP, one (7%) had hypertrophic LP, and one (7%) had inverted LP. Notably, there were two (8%) cases of lupus erythematosus/LP overlap. Moreover, six (25%) patients presented with nail alterations and chromonychia due to LP. Regarding hepatitis C serology, 20 patients (83%) had documented serology for hepatitis C, but only one patient (4%) had a positive serology, underwent treatment 5 years before the appearance of lesions and currently has a negative serology (Table 1).

Discussion

Our findings show that patients with higher phototypes have a higher prevalence of LP, which is consistent with data in the literature[10,11]. Notably, hypertension and diabetes were highly prevalent among our patients with LP. In several studies, dyslipidemia is associated with LP, but diabetes and hypertension are not; this may be attributed to metabolic syndrome alterations, which is a known risk factor for LP and other inflammatory dermatoses such as psoriasis[12,13].

From 2000 to 2021, 279,872 confirmed cases of hepatitis C were reported in Brazil; however, there is a decreasing trend in the number of cases. In 2016, there were 25,324 reported cases of hepatitis C, with a prevalence of 1.22%/100,000 inhabitants. In 2019 before the COVID-19 pandemic, there were 23,111 reported cases of hepatitis C, with a prevalence of 1.09%/100,000 inhabitants[14]. The decrease in the number of cases may be attributed to the introduction of antiretroviral drugs capable of curing the disease, which are distributed free of charge by the unified health system.

Although an association between LP and hepatitis C were reported by several studies, variables, such as the location where the studies were conducted, should be considered. In countries with a higher prevalence of hepatitis C, a greater association between the two diseases was reported. Meanwhile, there are authors who argue that the association between hepatitis C and LP may be the result of variants of the virus found only in certain geographic regions[7,15]. Despite the know association between LP and hepatitis C, we did not find an association between the two diseases.

In our study, most of the patients were women over 50 years old. Additionally, there was a high prevalence of comorbidities, including hypertension and diabetes, and smokers among the study population. Smoking is considered to be associated with oral LP[10]; in our study, smoking was associated with a greater predisposition for the cutaneous form of LP. The most evident LP subtype in our study was the classical cutaneous subtype, followed by the nail and oral subtypes.

The limitations of our study were the limited sample size and short analysis time. Oral biopsies were rarely performed and could justify the reduced number of oral variants.

Conclusion

Hepatitis C virus is reported to be an etiological agent of LP, suggesting that cutaneous and mucosal lesions may be caused by either the direct action of the virus or by an induced immune response[7]. However, in our sample, there was only one case of LP with a previous hepatitis C, and this patient developed LP 5 years after completing antiviral treatment.

Further studies are suggested to elucidate both the association and etiology. The association between the two diseases is controversial and varies according to the literature used as a reference.

Funding

None.

Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

References

1. Schwager Z, Stern M, Cohen J, Femia A. Clinical epidemiology and treatment of lichen planus: a retrospective review of 2 tertiary care centers. J Am Acad Dermatol. 2019;81:1397–9.
2. Canto AM, Müller H, Freitas RR, da Silva Santos PS. Líquen plano oral: diagnóstico clínico e complementar. An Bras Dermatol. 2010;85:669–75.

3. LI C, Tang X, Zheng X, Ge S, Wen H, Lin X, *et al*. Global prevalence and incidence estimates of oral lichen planus: a systematic review and meta-analysis. JAMA Dermatol. 2020;156:172–81.
4. Gorouhi F, Davari P, Fazel N. Cutaneous and mucosal lichen planus: a comprehensive review of clinical subtypes, risk factors, diagnosis, and prognosis. Sci World J. 2014;2014:742826.
5. Arnold DL,Krishnamurthy K. Lichen Planus In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022.
6. Azulay-Abulafia L *et al*. Atlas de Dermatologia – Da semiologia ao diagnóstico – 3ª edição, Rio de Janeiro, 2020;689–90.
7. Guerreiro TDT, Machado MM, Freitas THP. Associação entre líquen plano e infecções pelo vírus da hepatite C: um estudo prospectivo envolvendo 66 pacientes da clínica dermatológica da Santa Casa de Misericórdia de São Paulo. An Bras Dermatol. 2005;80:475–80.
8. Rocha MR, Lins L, Cattony AC. Associação entre líquen plano e o vírus da hepatite C: um estudo de metanálise. Rev Port Estomatol Med Dent Cir Maxilofac. 2018;59:2–9.
9. Ronald Rapini, Dermatopatologia Prática – 2ª edição – Rio de Janeiro, Brasil Capitulo 2; 56: Elsevier 2013.
10. Silverman S, Gorsky M, Lozada-Nur F, Giannotti K. A prospective study of findings and management in 214 patients with oral lichen planus. Oral Surg Oral Med Oral Pathol. 1991;72:665–70.
11. Kanwar AJ, Dogra S, Handa S, Parsad D, Radotra BD. A study of 124 Indian patients with lichen planus pigmentosus. Clin Exp Dermatol. 2003;28:481–85.
12. Aryanian Z, Shirzadian A, Hatami P, Dadras H. High incidence of metabolic syndrome components in lichen planus patients: a prospective cross-sectional study. Int J Clin Pract. 2022;2022:7184678.
13. González-Moles MÁ, Warnakulasuriya S, González-Ruiz I, González-Ruiz L, Ayén Á, *et al*. Worldwide prevalence of oral lichen planus: a systematic review and meta-analysis. Oral Dis. 2021;27:813–28.
14. Gisondi P, Fostini AC, Fossà I, Girolomoni G, Targher G. Psoriasis and the metabolic syndrome. Clin Dermatol. 2018;36:21–28.
15. MS/SVS/DCCI - Departamento de Doenças de Condições Crônicas e Infecções Sexualmente Transmissíveis. Notas:(1) Dados até 31/12/2019; disponíveis em http:// indicadoreshepatites.aids.gov.br/, acessados em 05/09/2022.

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ORIGINAL ARTICLE

Pediatric dermatology: nosological and consultations profile in a hospital complex in southern Brazil

Dermatologia pediátrica: perfil nosológico e de consultorias em um complexo hospitalar no sul do Brasil

Iago Gonçalves-Ferreira[1,2,a], Ana E. Kiszewski-Bau[1,2], Magda B. Weber[1,2], Lucas A. Bulcão[3], Camila S. Almeida[4], and Renan R. Bonamigo[1,5]*

[1]Dermatology Service, Santa Casa de Misericordia de Porto Alegre; [2]Department of Dermatology, Federal University of Health Sciences of Porto Alegre; [3]Faculty of Medicine, Federal University of Health Sciences of Porto Alegre; [4]Faculty of Medicine, University of Caxias do Sul; [5]Faculty of Medicine, Federal University of Rio Grande do Sul. Porto Alegre, Brazil.

[a]*ORCID: 0000-0002-4695-1982*

Abstract

Objective: The study aimed to analyze the profile of dermatoses and Dermatology consultations in a pediatric hospital in southern Brazil. **Method:** This descriptive and quantitative study was conducted from the analysis of admissions, hospital referrals, and dermatology consultations of pediatric inpatients from August 2018 to January 2020. The researchers performed an investigation in three phases: analysis of pediatric hospitalizations with dermatological diagnosis (phase 1), analysis of dermatology consultations referrals (phase 2), and analysis of dermatology consultations (phase 3). **Results:** Throughout the 18-month period analyzed, the authors identified 12,656 pediatric hospitalizations, 266 hospital referrals, and 167 dermatology consultations. Hospital dermatoses evidenced a prevalence of 6.8%, with "cellulitis" (L03) and "abscess" (L02) as the main conditions. In dermatology consultations, "dermatitis and eczema" and "skin infections" were the main groups of cutaneous disorders, whereas "atopic dermatitis" (L20) and "drug eruptions" (L27) were the main skin diseases. Corticoids, moisturizers, and antibiotics were the most recommended therapies by dermatologists. **Conclusion:** From this study, authors evidenced the prominence of inflammatory and infectious cutaneous conditions in children and adolescent populations. Moreover, vulnerabilities and shortcomings of the dermatology consultations process were also found, indicating the need for evaluations and enhancements, mainly regarding clinical data of referrals.

Keywords: Dermatology. Epidemiology. Hospitalization. Pediatrics. Skin diseases.

Resumo

Objetivo: O estudo teve como objetivo analisar o perfil das dermatoses e consultas de Dermatologia num hospital pediátrico do sul do Brasil. **Método:** Este estudo descritivo e quantitativo foi realizado a partir da análise das internações, encaminhamentos hospitalares e consultas de Dermatologia de pacientes pediátricos internados no período de agosto de 2018 a janeiro de 2020. Os pesquisadores realizaram uma investigação em três fases: análise de dermatoses pediátricas hospitalares (fase 1); análise de encaminhamentos de consultas de Dermatologia (fase 2) e análise de consultas de Dermatologia (fase 3). **Resultados:** Ao longo dos 18 meses analisados, os autores identificaram 12.656 internações pediátricas, 266 encaminhamentos

***Corresponding author:**
Iago Gonçalves-Ferreira
E-mail: iago_goncalves14@hotmail.com

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hospitalares e 167 consultas de Dermatologia. As dermatoses hospitalares evidenciaram prevalência de 6.8%, sendo 'Celulite' (L03) e 'Abscesso' (L02) as principais condições. Nas consultas de Dermatologia, 'Dermatite e eczema' e 'Infeções cutâneas' foram os principais grupos de distúrbios cutâneos, enquanto 'Dermatite atópica' (L20) e 'Erupções medicamentosas' (L27) foram as principais doenças de pele. Corticoides, hidratantes e antibióticos foram as terapias mais recomendadas pelos dermatologistas. **Conclusão:** A partir deste estudo, os autores evidenciaram a proeminência de quadros inflamatórios e infeciosos cutâneos em populações de crianças e adolescentes. Além disso, também foram encontradas vulnerabilidades e deficiências no processo de consultas de Dermatologia, indicando a necessidade de avaliações e aprimoramentos, principalmente quanto aos dados clínicos dos encaminhamentos.

Palavras-chave: Dermatologia. Doenças de pele. Epidemiologia. Hospitalização. Pediatria.

Introduction

Skin diseases represent about 30% of pediatric consultations in health systems, with high prevalence in different levels of health care[1-4]. These conditions can have a great psychological and social impact on the affected individuals, impairing their quality of life and daily activities, especially in the pediatric population, which is more sensitive and vulnerable[5].

Dermatological disorders may present as primary cutaneous diseases, acute or chronic, as well as secondary manifestations of systemic conditions, which may exacerbate or spread, causing associated complications that can be life-threatening[6-8]. Thus, due to the potential risk to life, especially for children and adolescents, such clinical conditions may require hospitalization, being initially managed by pediatric hospital teams[6-8].

Considering the particularities of skin manifestations in children and adolescent populations, pediatricians may demonstrate a certain degree of difficulty with their diagnosis and treatment[2,9,10]. Hence, dermatology can offer important contributions to inpatient care, providing backing to the management of pediatric patients by performing hospital consultations[11].

Thus, in view of the relevance of dermatology in hospital settings, it is pertinent to comprehend the profile of dermatologic consultations, identifying clinical practices, diagnostic and therapeutic patterns, as well as contributions to pediatric services. Therefore, this study aimed to analyze the profile of pediatric consultations performed by a dermatology service in a hospital complex in Southern Brazil.

Method

This descriptive and quantitative study was conducted from the analysis of admissions, hospital referrals, and dermatology consultations of inpatients admitted to Hospital da Criança Santo Antônio, the pediatric segment of the hospital complex Santa Casa de Misericordia de Porto Alegre, in Southern Brazil. The research was approved by the Human Research Ethics Committee of the institution and included hospitalization data from 1st August 2018 to 31st January 2020.

From a preliminary data collection, we identified 12,656 pediatric hospitalizations and 816 consultation referrals forwarded to the dermatology Service. Subsequently, we carried out an exploratory analysis, which excluded suspended requests and duplicate referrals from the same medical speciality. Posteriorly, we proceeded to an investigation organized into three analytical phases: analysis of pediatric hospitalizations with dermatological diagnosis (phase 1), analysis of dermatology consultations referrals (phase 2), and analysis of dermatology consultations (phase 3). It is worth mentioning that, based on the analysis of consultations referrals, we performed an additional exclusion procedure of duplicate referrals, even those from different specialties, in order to proceed with the analysis of dermatology consultations.

Considering this research arrangement, we analyzed three groups of variables: "pediatric skin diseases", reported by inpatient pediatric teams; "profile of consultations referrals" (hospital sector, pediatric subspecialties, patients' age and sex, clinical data, and diagnostic hypotheses) and "profile of dermatology consultations" (clinical description, complementary exams, dermatological diagnoses, therapeutic conducts, and recommend follow-ups).

Regarding consultation referrals, according to W Huang and Chong S[12], we established four analysis parameters: "morphology of skin lesions," "distribution of skin lesions," "evolution of clinical condition," and "diagnostic hypothesis or purpose of referral." Dermatological diagnoses were established according to the International Classification of Diseases (ICD-10).

With respect to follow-up recommendations, we considered "outpatient follow-up" for those hospital consultations whose duration of dermatology assistance was equal to or < 7 days, followed by recommendations for outpatient follow-up. In contrast, "inpatient + outpatient

Table 1. Pediatric hospital dermatoses and dermatological consultations referrals

	n	%
Pediatric hospitalizations	12.656	100.0
ICD diagnosis of skin diseases among pediatric hospitalizations	865	6.8
Referrals for dermatological consultations	266	2.1
Dermatological consultations	167	1.3
Major skin diseases ICDs		
L03-Cellulitis and acute lymphangitis	124	14.3
L02-Cutaneous abscess. furuncle and carbuncle	95	11.0
D69-Purpura	76	8.8
L50-Urticaria	56	6.5
L90-Atrophic disorders of skin	47	5.4
L98-Other disorders of skin and subcutaneous tissue	44	5.1
L01-Impetigo	31	3.6
L20-Atopic dermatitis	31	3.6
L72-Follicular cysts	30	3.5
D18-Hemangioma and vascular malformations	29	3.4

follow-up" were considered hospital consultations whose dermatology assistance duration was longer than 7 days, with a recommendation for outpatient follow-up after completion.

In statistical analysis, categorical and numerical variables were represented descriptively by measures of dispersion and frequencies, whereas the groups of hospital dermatoses were analyzed by chi-squared test (X^2), considering p-value ≤ 5% statistically significant.

Results

Dermatological hospitalizations and consultations referrals

During the period of August 2018-January 2020, we identified 12,656 pediatric hospitalizations, with 865 dermatological ICDs registered, which represents 6.8% of the total hospitalizations. The main dermatological ICDs were "cellulitis and acute lymphangitis" (14.3%), "cutaneous abscess, furuncle, and carbuncle" (11.0%), and "purpura" (8.8%) (Table 1).

Dermatology referrals included 266 referrals from hospital teams, either from the pediatric ward (54.5%) or the pediatric emergency (37.6%) as the main requesting hospital sectors. Most of the referrals originated from general pediatrics (73.3%) and pediatric oncology (8.3%). The majority of pediatric patients were hospitalized under public health system coverage (66.1%) (Table 2).

In relation to referrals' information, a significant portion of them did not present data about clinical conditions (48.5%). The location of skin lesions was the most referred clinical data (30.0%). Only 3.7% of referrals reported the four clinical parameters analyzed, whereas diagnostic hypotheses were indicated in only 28.5% of the dermatology referrals (Table 2).

Profile of dermatology consultations

After preliminary analysis and duplicate referrals exclusion, we identified 167 pediatric consultations performed by the dermatology team during the 18-month period, with a response time of < 24 hours for most of the evaluations (80%). Most inpatients were males (56.9%), "younger than 1 year" (19.2%), or "11-14 years" (19.2%). Most evaluations led to single diagnoses (77.8%), with "dermatitis and eczema" and "skin infections" standing out as the most prominent groups of dermatoses, with 38.7 and 31.2%, respectively (Table 3).

Regarding the profile of dermatoses by age groups, we observed a higher prevalence of "Skin infections" among neonates, infants, and preschoolers, whereas "dermatitis and eczema" were most frequent among schoolers and adolescents (Figure 1). About dermatological ICDs, "scabies" (B86) and "impetigo" (L01) stood out among the major skin diseases at younger ages, whereas "drug eruptions" (L27) were more relevant with advancing age, particularly in adolescence. "Atopic dermatitis" (L20) exhibited high prevalence in all age groups but with greater expression in preschoolers and schoolers (Table 4).

Laboratory tests (29.3%) and skin biopsies (10.8%) were the main requested complementary exams. Skin biopsies presented anatomopathological reports in concordance with the clinical diagnoses of dermatology teams in 66.6% of the evaluations (n = 12/18). "Bacterial cultures" were requested only in 6% (n = 10/167) of hospital consultations, with *Staphylococcus aureus* as the most prevalent etiologic agent (40%; n = 4/10).

With respect to dermatologists' management, corticoids were the most recommended drugs in consultations (35.7%), with a predominance of topical presentations (59.3%), followed by moisturizers (26.3%) (Table 3). Antibiotics were indicated in 22.7% of the dermatology evaluations, highlighting the systemic presentation (n = 33/86.8%), mainly oxacillin (n = 14/38; 36.8%) and cephalexin (n = 9/38; 23.7%).

Table 2. Profile of hospital dermatological consultations referrals

	n	%
Hospital sector		
Pediatric ward	145	54.5
Pediatric intensive care unit	17	6.4
Pediatric emergence	100	37.6
Pediatric surgery unit	4	1.5
Sector character		
Public health system	176	66.1
Private health system	69	25.9
Mixed	21	7.9
Pediatric subspecialties		
General pediatrics	195	73.3
Intensive pediatrics	9	3.4
Pediatric endocrinology	1	0.4
Pediatric gastroenterology	4	1.5
Pediatric hematology	8	3.0
Pediatric infectology	11	4.1
Pediatric oncology	22	8.3
Pediatric pneumology	3	1.1
Pediatric nephrology	5	1.9
Pediatric neurology/neurosurgery	6	2.2
Pediatric surgery	1	0.4
Neonatology	1	0.4
Clinical information on referrals		
No variable described	129	48.5
1 variable described	54	20.3
2 variables described	49	18.4
3 variables described	24	9.0
4 variables described	10	3.7
Description of skin lesions	56	21.0
Location of skin lesions	80	30.0
Time of clinical evolution	22	8.3
Diagnostic hypothesis	74	27.8
Referral status		
Consultation performed	167	62.8
Duplicate referral	53	19.9
Suspended or lost referral	46	17.3
Total	266	100.0

Table 3. Profile of hospital dermatological consultations

Total	167 consultations	
Monthly average	9.3 consultations	
Daily average	0.3 consultations	
	n	**%**
Hospital sector		
Pediatric ward	87	52.1
Pediatric intensive care unit	6	3.6
Pediatric emergence	73	43.7
Pediatric surgery unit	1	0.6
Patient demographics		
Gender		
Male	95	56.9
Female	72	43.1
*Age group**		
Neonates	16	9.6
Infants	16	9.6
Toddlers	23	13.8
Preschoolers	27	16.2
Schoolers	29	17.4
Adolescents	56	33.6
Dermatological diagnoses**		
One diagnosis	130	77.8
Two diagnoses	30	18.0
Three diagnoses	3	1.8
Complementary exams***		
Skin biopsy	18	10.8
Bacterial culture	10	6.0
Direct mycological examination	9	5.4
Tzanck's smash	3	1.8
Imaging exams	8	4.8
Laboratory exams	49	29.3
Therapeutic recommendations		
Antibiotics		
Yes	38	22.7
Topical	5	3.0
Systemic	33	19.7
No	129	77.3
Corticosteroids		
Yes	59	35.3
Topical	35	20.9
Systemic	24	14.4
No	108	64.7
Antifungals		
Yes	10	6.0
Topical	7	4.2
Systemic	3	1.8
No	157	94.0

(Continues)

Table 3. Profile of hospital dermatological consultations *(continued)*

	n	%
Antiviral		
Yes	6	3.6
Oral acyclovir	3	1.8
Intravenous acyclovir	3	1.8
Other antivirals	0	0.0
No	161	96.4
Antiparasitic*		
Yes	19	11.4
Permethrin	1	0.6
Ivermectin	4	2.4
Permethrin + ivermectin	7	4.2
Sulfur 6%	7	4.2
No	148	88.6
Moisturizer		
Yes	44	26.3
Specific	23	13.8
Generic	21	12.5
No	123	73.7
Total	167	100.0

*Age groups: neonates (under 1 month); infants (2-11 months); toddlers (1-2 years); preschoolers (3-5 years); schoolers (6-10 years); adolescents (11-17 years).
**Due to the multiple diagnoses, the total of 167 consultations corresponds to 199 dermatological diagnoses.
***Multiple response variables.

"Outpatient follow-up" and "inpatient and outpatient follow-up" were the leading orientations of dermatology follow-up, appearing in 35 and 32% of hospital consultations, respectively. Furthermore, 4.8% (n = 8/167) of dermatological consultations presented loss of follow-up during the dermatology hospital assistance, whereas 28.7% (n = 48/167) were managed and discharged by the dermatology team without the need for additional outpatient follow-up (Figure 2).

Discussion

Although dermatology reveals an essentially outpatient character, the speciality provides significant contributions to the management of skin diseases in hospital settings, both for adult and pediatric patients[10,13]. From this perspective, our findings evidenced the relevance of hospital dermatoses in a pediatric population, representing 6.8% of hospital diagnoses, in line with a similar American study, which pointed out a prevalence of 4.2%[14]. Thus, proper management of these cutaneous conditions is essential to prevent complications and poor prognosis.

In contrast, hospital dermatoses are commonly assisted by non-dermatologists' teams, which often do not properly diagnose these clinical conditions. In view of this tendency, dermatology consultations figure as a meaningful resource to support the assistant medical teams[9]. From our findings, we identified 266 pediatric referrals to dermatology, most of them coming from "general pediatrics" and from pediatric wards and emergency sectors, as noted in previous studies[2,4,10].

In the pediatric population, likewise in adults, hospital dermatoses often manifest as acute or life-threatening conditions, entering hospitals through emergency services. According to Alba-Rojas EL et al.[15], skin disorders are among the ten most common classes of diseases in pediatric emergencies. In accordance with such authors, we observed 37.6% of dermatology consultation referrals originated from the emergency department, a higher prevalence than in other studies in India[4,10] and Turkey[2].

Regarding consultation referrals, despite the relevance of clinical information for the efficient support of consultant teams, about half of referrals to Dermatology did not present any clinical data, which may suggest a certain difficulty for pediatricians in skin disorders management. On the other hand, in referrals with clinical information, the location of cutaneous lesions was the most reported data, although, in most of them, few

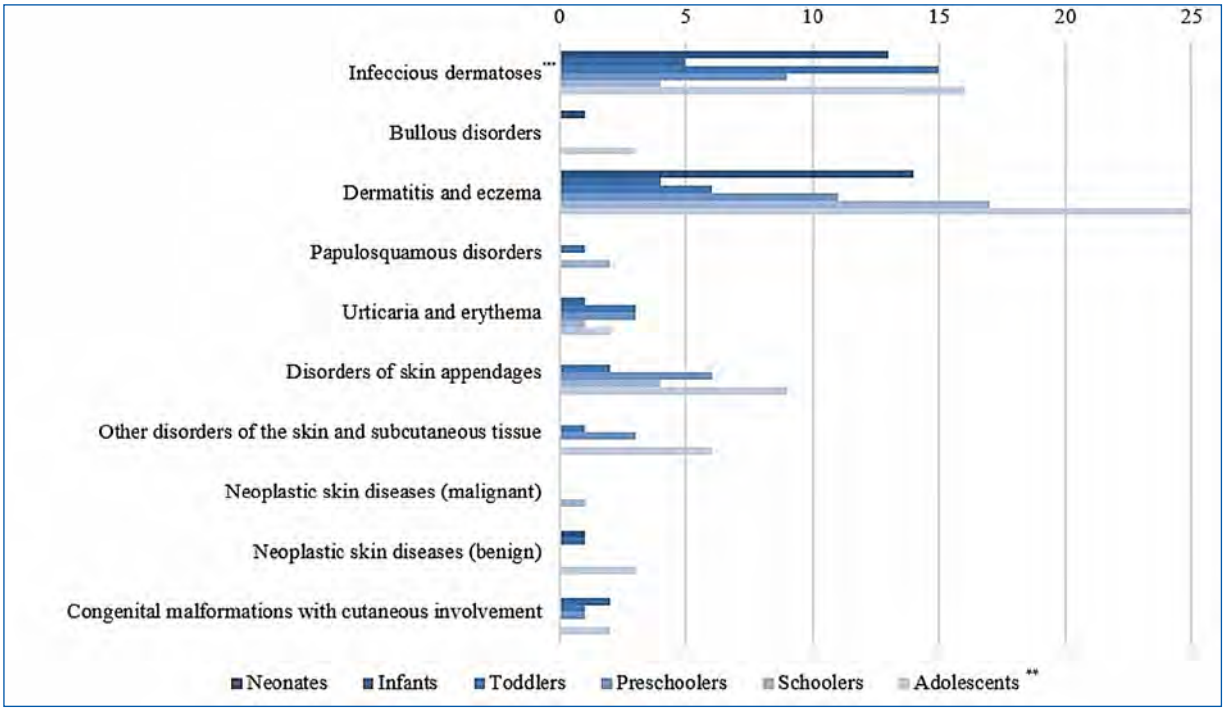

Figure 1. Groups of skin diseases in dermatological consultations, by age groups*.
*Total of 167 consultations corresponds to 199 dermatological diagnoses; chi-square test 63,502, p = 0,029.
**Age groups: neonates (under 1 month); infants (2-11 months); toddlers (1-2 years); preschoolers (3-5 years); schoolers (6-10 years); adolescents (11-17 years).
***Infectious dermatoses and ICDs: bacterial infections (L00, L01, L02, L03, L08, A30, A46, A53); viral infections (B00, B01, B02, B07, B08, B97); fungal infections (B35, B36, B37, B42); parasitic infections and infestations (B85, B86, B87).

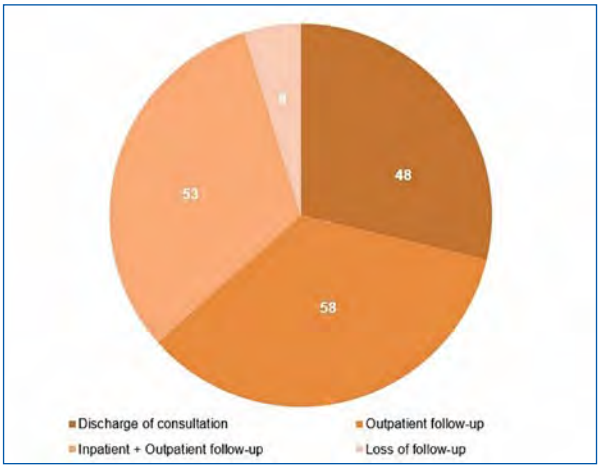

Figure 2. Follow-up recommendations of dermatology consultations*.
*Outpatient follow-up' consists of dermatological consultations whose duration of dermatology assistance was ≥ 7 days and with recommendation for outpatient follow-up after completion. "Inpatient + outpatient follow-up" included dermatological consultations whose dermatology assistance duration was longer than 7 days and with a recommendation for outpatient follow-up after completion.

features were mentioned. Inconsistencies in hospital referrals to Dermatology were also identified by Daye M et al.[2], from a study in a Turkish institution.

In view of these findings, we highlighted the relevance of adequate teaching of dermatology throughout the medical course, mainly in an internship, providing the development of clinical and examination skills in the approach to skin diseases.

Dermatology consultations: epidemiology of hospital skin diseases

Throughout the 18-month period analyzed, dermatology teams performed 167 hospital consultations, with a higher prevalence of adolescent and schooler inpatients, converging with a study in a Brazilian university hospital[16]. Conversely, this trend differs from findings in a Turkish pediatric hospital, where infants and preschool were the most frequent age groups[9].

These contrasts can be related to demographic and epidemiological differences between the populations of such countries or even reflect methodological divergences insofar as studies with pediatric populations

Table 4. Major diagnostic ICDs of dermatological consultations by age groups

		n	%
L20-atopic dermatitis		32	23.7
L27-drug eruptions		23	17.0
L01-impetigo		18	13.3
B86-scabies		17	12.6
L70-acne		10	7.4
L21-seborrheic dermatitis		10	7.4
B00-herpesvirus infections		9	6.7
L50-urticaria		6	4.4
L30-unspecified dermatitis		6	4.4
Q89-congenital malformations		4	3.0
ICDs of dermatological consultations			
Neonates Under 1 month	L21-seborrheic dermatitis	8	27.6
	B86-scabies	6	20.7
	L01-impetigo	4	13.8
	L20-atopic dermatitis	4	13.8
	B081-molluscum contagiosum	1	3.4
Infants 2-11 months	B86-scabies	2	15.4
	L20-stopic dermatitis	2	15.4
	B00-herpesviral infections	1	7.7
	B87-myiasis	1	7.7
	D18-hemangioma and lymphangioma	1	7.7
Toddlers 1-2 years	B86-scabies	5	17.2
	L01-impetigo	3	10.3
	B081-molluscum contagiosum	2	6.9
	L20-atopic dermatitis	2	6.9
	L53-other erythematous conditions	2	6.9
Preschoolers 3-5 years	L20-atopic dermatitis	6	18.2
	L27-drug eruptions	4	12.1
	L01-impetigo	3	9.1
	L50-urticaria	3	9.1
	B00-herpesviral infections	2	6.1
Schoolers 6-10 years	L20-atopic dermatitis	10	30.3
	L01-impetigo	4	12.1
	L27-drug eruptions	4	12.1
	L30-unspecified dermatitis	2	6.1
	L40-psoriasis	2	6.1
Adolescents 11-17 years	L27-drug eruptions	13	19.7
	L20-atopic dermatitis	8	12.1
	L70-acne	8	12.1
	B00-herpesviral infections	6	9.1
	L01-impetigo	3	4.5

*International Classification of Diseases (ICD-10).

Table 5. Literature review about Pediatric Hospital Dermatology

Author (year)	Institution	City (Country)	Duration	Period of time	Casuistry	Main groups of skin diseases (%)
Ferreira et al. (Present study)	Federal University of Health Sciences of Porto Alegre / Santa Casa de Misericordia de Porto Alegre	Porto Alegre (Brazil)	18 months	August, 2018-January, 2020	167 patients	Dermatitis and eczema (38.7) Skin infections (31.5) Disorders of skin appendages (10.5)
Garg et al.[4]* (2019)	Lady Hardinge Medical College and Associated Hospitals	New Delhi (India)	17 months	November, 2015-March, 2017	525 patients	Skin infections (58.6) Eczema (17.6) Urticaria (8.3)
Srinivas et al.[10] (2015)	Indira Gandhi Institute of Child Health	Bangalore (India)	42 months	January, 2010-June, 2013	486 patients	Skin infections (23.7) Genodermatoses (11.9) Drug reactions (8.0)
McMahon et al.[16] (2013)	Children's Hospital of Philadelphia	Philadelphia (USA)	52 months	January, 2006-April, 2010	427 patients	Miscellaneous (41.0) Skin infections (19.0) Dermatitis (15.7)
Afsar[9] (2017)	Dr. Behcet Uz Children's Hospital	Izmir (Türkiye)	76 months	January, 2004-April, 2010	539 patients	Allergic skin diseases (47.1) Skin infections (14.7) Systemic disorders with skin manifestations (10.2)
Peñate et al.[18] (2012)	Hospital Universitario Insular de Gran Canaria	Las Palmas de Gran Canaria (Spain)	10 years	January, 2000-January, 2009	387 patients	Inflammatory skin diseases (38.5) Skin infections (18.3) Congenital anomalies (6.9)
Daye et al.[2] (2019)	Necmettin Erbakan University Meram Medical Faculty	Konya (Türkiye)	1 year	September, 2016-September, 2017	628 patients	Skin infections (32.1) Eczema (28.2) Miscellaneous (21.5)

*The authors included outpatients and inpatients in the study casuistry.

tend to adopt different compositions of age groups, hampering comparative analysis. Thus, if we consider age, one-third of dermatology consultations addressed 2-year-old or younger patients, which may represent an immunological immaturity and a higher life-threatening risk in the early stages of life[9].

Regarding the profile of dermatoses, the main groups of diagnoses were "dermatitis and eczema" and "skin infections", agreeing with previous investigations[2,4,10,17] (Table 5). Hence, "drug eruptions" (L27) and "atopic dermatitis" (L20) figured as the most prevalent cutaneous disorders assisted by dermatology consultations, followed by "impetigo" (L01) and "herpes virus infections" (B00), which were the most frequent skin infections.

Atopic dermatitis is one of the most frequent dermatological causes of pediatric hospitalizations, particularly in preschool and school ages[1,2,9,18,19]. This condition may evolve with recurrent exacerbations, presenting eczema, erythroderma, and secondary infections, then requiring hospital care[1,20]. With this in mind, the high prevalence of atopic dermatitis and skin infections can suggest their concomitance, as asserted by Narla S and Silverberg JI[20], who pointed out the greater susceptibility to bacterial and viral infections among patients with atopic dermatitis. According to Storan ER et al.[18], timely pediatric hospitalizations can contribute both to managing atopic dermatitis, as well as to support parents and caregivers in the adherence to medical and non-medication measures for controlling the disease. Nonetheless, on the other hand, hospital environments may also represent health risks, mainly due to recurrent administration of medications and exposure to nosocomial bacteria.

During the hospital stay, medications are often necessary and widely prescribed by assistant teams, especially in systemic forms. However, the administration of multiple drugs, along with debilitated patients' conditions, increases the risk of drug reactions[2]. Drug reactions can induce a broad range of clinical manifestations, which often involve the skin, namely morbilliform exanthema, Stevens-Johnson syndrome, toxic epidermal necrolysis, among others[10]. Corroborating this perspective, we observed a high prevalence of drug eruptions among pediatric inpatients, particularly in the adolescent group.

Furthermore, the skin fragility of early pediatric age groups also increases the risk of iatrogenic lesions, usually associated with healthcare, including dressings, vascular punctures, and prolonged decubitus[21]. Thus, iatrogenic injuries can often suffer complications such as contact dermatitis, ulcers, secondary skin infections, and vascular cutaneous disorders[22], which could be a possible reason for the preponderance of "cellulitis and acute lymphangitis," (L03) "cutaneous abscess, furuncle, and carbuncle," (L02) and "purpura" (D69), as the main dermatological diagnoses registered by pediatric assistant teams.

Dermatology consultations: diagnosis and recommendations

In view of the variety of skin disorders, dermatology can perform a supporting role to pediatric hospitalists, contributing to avoiding inconsistent diagnosis and incorrect treatments, which would lead to iatrogenic complications and/or drug reactions, mainly in the pediatric population[2]. Thus, the exchange of knowledge and practices among dermatologists and pediatricians can confer a qualification for the assistance of complex skin conditions[23].

Moreover, dermatologists can also contribute by performing complementary exams, such as skin biopsy and direct mycological examination[1,9]. Considering this assumption, we noted the main complementary exams in hospital consultations: laboratory tests (29.3%) and skin biopsies (10.8%), the latter performed by the dermatology team. Skin biopsies were reduced in relation to previous studies—in India[10] (17.5%) and the United States[23] (35%)—which may be related to different epidemiological profiles of these settings, then necessitating further investigation.

Concerning dermatology recommendations, topical presentations were the main form of medication, in concordance with the literature[2,9]. Diverging from research in Turkish hospital[2], which pointed out moisturizers and antihistamines as major prescribing medications, our findings demonstrated topical corticoids and systemic antibiotics.

Although this study did not conduct a comparative analysis between non-dermatologists and dermatologists' managements, Daye M et al.[2] highlighted a tendency for assistant teams to prescribe treatments before dermatology evaluation in about a third of consultations, then to establish inadequate treatments in half of those hospitalizations.

About two-thirds of dermatology consultations recommended an outpatient follow-up, a higher propensity than reported by Moon AT et al.[24] (48.1%) and Srinivas SM et al.[10] (35.8%). Notwithstanding, disease severity and patients' vulnerability greatly contribute to follow-up recommendations; thus, further studies are demanded to identify relations between epidemiological profiles and follow-up among different scenarios.

Pediatric dermatology and pediatrics: dialogue and contributions

Considering pediatric hospital dermatoses, both in dermatology consultations and in general pediatric wards, we noted that pediatricians demonstrated a tendency to diagnose more common and less complex cutaneous conditions, whereas dermatologists usually established more specific and defiant diagnoses, including atopic dermatitis, acne, psoriasis, and drug eruptions.

Nonetheless, our findings revealed severe cutaneous infectious—relatively common in pediatric populations—also emerged in dermatology consultations, such as scabies, impetigo, herpes virus infections, and molluscum contagiosum. This trend suggests a prominent need for training pediatricians on the diagnosis and management of dermatological disorders[9]. Furthermore, Dermatology consultations also represent a valuable teaching-learning opportunity, favoring the exchange of experiences and improvement of clinical practices[17].

From this perspective, Daye M et al.[2] and Garg T et al.[4] recommended integration strategies among pediatrics and dermatology in the shape of seminars, courses, and clinical case discussions. Thus, by proposing and developing these educational activities, a field of shared knowledge can be fashioned: hospital pediatric dermatology[17].

Conclusion

From this study, we outlined the profiles of dermatoses and dermatology consultations in a pediatric hospital, evidencing the prominence of inflammatory and infectious cutaneous conditions in children and adolescent populations. Moreover, vulnerabilities and shortcomings of the dermatology consultations process were also found, indicating the need for evaluations and enhancements, mainly regarding clinical data of referrals.

The acute character of various dermatoses, although not severe in many cases, reinforces the importance of both proper clinical management of cutaneous conditions, as well as the establishment of adequate criteria for

dermatology consultation referrals and hospital admissions for those skin disorders.

About study limitations, we state the retrospective character of this research, based on the analysis of referrals' registration and medical records, which may eventually present inaccuracies and/or absence of data. In addition, since dermatological diagnoses were established by dermatology teams, they can reveal a certain degree of subjectivity, strongly influenced by dermatologists' skills.

In view of the findings and considerations presented through this study, the relevance of dermatology for hospital assistance became evident, which can provide valuable contributions to other medical specialties, including pediatrics.

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Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors have obtained approval from the Ethics Committee for the analysis and publication of routinely acquired clinical data, and informed consent was not required for this retrospective observational study.

References

1. Miotto IZ, Bessa VR, Vasconcelos LB A, Samorano LP, Rivitti-Machado MC, Oliveira ZNP. Pediatric dermatoses pattern at a Brazilian reference center. J Pediatr (Rio J). 2021;97:211–8.
2. Daye M, Temiz SA, Durduran Y, Balevi Ş, Dursun R, Ataseven A, et al. Analysis of consultation cases referred from Pediatrics Department to Dermatology Outpatient Clinic: retrospective study. Clin Exp Heal Sci. 2019;9:300–3.
3. Liang Y, Chen YL, Zhao MT, Wang ZY, Li L, Zhang B, et al. Pediatric dermatology-critical approach to the new treatments. Dermatol Ther. 2018;32:e12801.
4. Garg T, Ahmed R, Basu S, Chander R. Clinical spectrum of dermatological disorders in children referred from pediatrics department. Indian J Paediatr Dermatol. 2019;20:212–8.
5. Nanda A, Al-Hasawi F, Alsaleh QA. A prospective survey of pediatric dermatology clinic patients in Kuwait: an analysis of 10,000 cases. Pediatr Dermatol. 1999;16(1):6–11.
6. Wolf R, Davidovici BB, Parish JL, Parish LC. Emergency Dermatology. First edit. Cambridge University Press; 2010. 378 p.
7. Cavero J. Características demográficas y clínicas de los pacientes evaluados en interconsulta dermatológica en un hospital nacional de Lima-Perú. Dermatologia Peru. 2017;27:75–8.
8. Rosenbach M, Wanat KA, Michelleti RG. Inpatient Dermatology. First Edit. Springer London; 2018. 407 p.
9. Afsar FS. Análisis de las interconsultas con dermatología pediátrica de pacientes hospitalizados en un hospital pediátrico universitario. Arch Argent Pediatr. 2017;115:E377–84.
10. Srinivas SM, Hiremagalore R, Venkataramaiah LD, Premalatha R. Pediatric dermatology inpatient consultations: a retrospective study. Indian J Pediatr. 2015;82:541–4.
11. Ko LN, Kroshinsky D. Dermatology hospitalists: a multicenter survey study characterizing the infrastructure of consultative dermatology in select American hospitals. Int J Dermatol. 2018;57:553–8.
12. Huang W, Chong WS. Patterns of inpatient dermatology referral and predictors of diagnostic accuracy in non-dermatologists in a Northern District hospital in Singapore. Int J Dermatol. 2015;55:546–52.
13. McMahon PJ, Yan AC. Inpatient consultative pediatric dermatology: an emerging need in an era of increasing inpatient acuity and complexity. Pediatr Dermatol. 2013;30:508–9.
14. Arnold JD, Yoon S, Kirkorian AY. Inpatient burden of pediatric dermatology in the United States. Pediatr Dermatol. 2018;35:602–6.
15. Alba-Rojas EL, Morán-Villaseñor E, Campos-Cabrera BL, Aguirre-Martínez IL, Vega-Rangel RV, Cazares-Ramírez E, et al. Diagnostic concordance between Pediatric Emergency Department physicians and dermatologists in a tertiary hospital in Mexico. Pediatr Dermatol. 2020;37:1113–8.
16. Ferreira FR, Nascimento LFC, Cirvidiu DC. Prevalence of pediatric dermatoses in a university hospital in southeastern Brazil. An Bras Dermatol. 2011;86:477–82.
17. Peñate Y, Borrego L, Hernández N, Islas D. Pediatric dermatology consultations: a retrospective analysis of inpatient consultations referred to the dermatology service. Pediatr Dermatol. 2012;29:117–8.
18. Storan ER, McEvoy MT, Wetter DA, El-Azhary RA, Hand JL, Davis DMR, et al. Pediatric hospital dermatology: experience with inpatient and consult services at the Mayo Clinic. Pediatr Dermatol. 2013;30:433–7.
19. Castelo-Soccio L, Mcmahon P. Pediatric dermatology. J Clin Aesthet Dermatol. 2017;10:S8–15.
20. Narla S, Silverberg JI. Management of atopic dermatitis in the inpatient setting. Curr Dermatol Rep. 2021;10:77–88.
21. Reddy K, Kogan S, Glick SA. Procedures and drugs in pediatric dermatology: iatrogenic risks and situations of concern. Clin Dermatol. 2011;29:633–43.
22. Ferreira IG, Weber MB, Bulcão LA, Bonamigo RR. The impact of skin diseases in hospital care and the contributions of dermatology. J Port Soc Dermatol Venereol. 2021;79:41–6.
23. McMahon P, Goddard D, Frieden IJ. Pediatric dermatology inpatient consultations: a retrospective study of 427 cases. J Am Acad Dermatol. 2013;68:926–31.
24. Moon AT, Castelo-Soccio L, Yan AC. Emergency department utilization of pediatric dermatology (PD) consultations. J Am Acad Dermatol. 2016;74:1173–7.

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REVIEW ARTICLE

Janus Kinase inhibitors in dermatology: a review

Inibidores da Janus Quinase na dermatologia: uma revisão

Bárbara Vieira-Granja[1] and Sofia Magina[1,2]*

[1]Departament of Dermatology and Venereology, Centro Hospitalar Universitário de São João; [2]Departament of Pharmacology and Therapeutics, Faculdade de Medicina da Universidade do Porto. Porto, Portugal.

Abstract

Janus Kinases (JAKs) are a subset of cytoplasmic protein tyrosine kinases (TYK), crucial for the initiation of signaling pathways activated by cytokines through phosphorylation and activation of the signal transducer and activator of transcription (STAT) proteins. Selective JAK inhibitors can simultaneously block the function of multiple cytokines and, consequently, the transcription of genes responsible for inflammation and the control of innate and adaptative immunity. These molecules play a foundational role in the underlying pathogenesis of multiple immune-related conditions such as atopic dermatitis (AD), rheumatoid arthritis, psoriatic arthritis, inflammatory bowel disease, and others. There is growing evidence that JAK inhibitors are efficacious in AD, alopecia areata (AA), psoriasis (PSO), and vitiligo. Additional evidence suggests that JAK inhibition may be broadly useful in dermatology, with early reports of efficacy in other conditions. They can be administrated orally; however, the concern for side effects has prompted the investigation into topical preparations that appear to be safe and well-tolerated and can be a promising alternative to oral formulations.

***Keywords*:** Alopecia areata. Atopic dermatitis. Janus Kinase. Psoriasis. Janus Kinases inhibitors. Vitiligo.

Resumo

As proteínas Janus Quinase (JAKs) correspondem a um conjunto de proteínas tirosina quinase citoplasmáticas ativadas por citocinas, que são cruciais para o início das vias de sinalização através da fosforilação e ativação do Transdutor de Sinal e Ativador de Proteínas de Transcrição (STATs). Os inibidores das JAKs podem bloquear simultaneamente a função de múltiplas citocinas, e consequentemente, a transcrição de genes responsáveis pela inflamação e pelo controlo da imunidade inata e adaptativa. Estas moléculas desempenham um papel fundamental na patogénese subjacente de várias condições relacionadas com o sistema imunológico, como na dermatite atópica (DA), artrite reumatoide, artrite psoriática, doença inflamatória intestinal e outras. Existe evidência crescente de que os inibidores das JAKs são eficazes na dermatite atópica, alopecia areata, psoríase e vitiligo. Estudos adicionais sugerem que a inibição das JAKs possa ser amplamente útil na Dermatologia, com relatos de eficácia noutras patologias. A administração pode ser por *via* oral, contudo a preocupação com os efeitos adversos motivou a investigação de formulações tópicas, que parecem ser seguras, bem toleradas e podem constituir uma alternativa promissora às formulações orais.

Palavras-chave: Alopecia areata. Dermatite atópica. Janus Quinase. Psoríase. Inibidores das Janus Quinase. Vitiligo.

***Corresponding author:**
Bárbara Vieira-Granja
E-mail: bgranja@campus.ul.pt

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Mechanism of action of the JAK-STAT pathway

The Janus Kinase (JAK) and signal transducer and activator of transcription (STAT) pathway is a ubiquitous intracellular signaling network that is involved in the signal transduction of numerous dermatologically relevant cytokines[1,2]. JAK family is composed of four members: JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2). The function of JAK proteins is associated with the type of cytokine that binds the receptors and they play a key role in cell growth, development and differentiation. They are especially found in immune and hematopoietic cells, such as lymphocytes, natural killer cells, and mast cells, but cytokine signaling is also important for the biology of nonimmune cells such as keratinocytes, fibroblasts, osteoblasts, synoviocytes, or endothelial cells. JAK1, JAK2, and TYK2 are involved in cell growth processes in different cell types, while JAK3 is critical to hematopoiesis[3]. Different JAKs are associated with specific cytokine receptors and influence different aspects of immune cell development and function. These proteins modulate the inflammatory process by activating intracytoplasmic transcription factors called STAT. STAT family influences DNA transcription and plays an important role in regulating gene expression, cell differentiation, proliferation, survival and apoptosis. This family is composed of seven proteins (STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b and STAT6); phosphorylated STATs dissociate from the receptor, translocate to the cell nucleus and regulate transcription either positively or negatively of thousands of different genes (Figure 1).

Thus, selective JAK inhibitors can simultaneously block the function of multiple cytokines and, consequently, the transcription of genes responsible for inflammation and the control of innate and adaptative immunity. Most cytokine receptors use a combination of JAKs for their activity, enabling the idea of targeting single JAKs. JAK inhibitors are divided into two generations, the first generation blocks more than one type of JAK, while the second generation is more specific and blocks only one type of JAK and consequently has fewer side effects[3]. The first-generation JAK inhibitors include tofacitinib, ruxolitinib (RUX), baricitinib, and oclacitinib, all of which are approved for use in humans, except oclacitinib[4]. Abrocitinib and upadacitinib are commonly referred to as selective JAK1 inhibitors[2,4].

Rational for the use of JAK-inhibitors in dermatology

The perpetuation of inflammation in diseased skin strongly relies on the interaction between cytokines, immune, and tissue cells propagating distinct inflammatory cascades. Differently from biologics that target cytokines by intravenous or subcutaneous injection, JAK inhibitors target cytokine signaling by either oral or topical administration. The latter way of application may minimize the risk of side effects. Topical JAK inhibitors do not bear the risk of skin atrophy or telangiectasia, as observed with long courses of topical corticosteroids[2]. There is growing interest in the potential use of these drugs in many dermatological diseases, such as alopecia areata (AA), vitiligo, and atopic dermatitis (AD). The cytokines involved in each of these diseases differ; however, in all three, the effects of cytokine binding are mediated through the JAK pathway, providing a rationale for JAK inhibition. Although there are many JAK inhibition under study, only some are approved for the treatment of dermatological diseases (Table 1).

Atopic dermatitis

Atopic dermatitis (AD) is a common chronic disease of the skin that has a great impact on a patient's quality of life. The disease can manifest at any age, but its prevalence is higher in children and adolescents. Clinically AD is characterized by the presence of pruriginous eczematous lesions, typically on flexural sites. This heterogeneous condition has a complex pathophysiology; historically AD is thought to be T helper 2 (Th2) dominated disease, but there is growing evidence that the immunological environment of AD is not solely defined by Th2 cells and related cytokines but also by cytokines linked to other Th cells responses such as INF-ϒ [(interferon-gamma) Th1], interleukin (IL)—17, IL-22 (Th17) and IL-33[2]. Given the diversity of cytokines implicated in the inflammatory process of AD, there is growing interest in JAK inhibition, which could interfere with multiple cytokines simultaneously.

Various cytokines relevant to the pathophysiology of AD, including IL-4, IL-13, IL-22, IL-31, and thymic stromal lymphopoietin, activate JAK1 containing heterodimeric receptors, thereby mediating Th2 cell differentiation[5]. Additionally, chronic itch is also directly mediated by neuronal JAK1 signaling, and IL-22 drives epidermal hyperplasia *via* JAK1. Together these findings suggest the importance of JAK1 signaling in the pathogenesis of AD[6]. JAK2 forms homodimeric receptor complexes

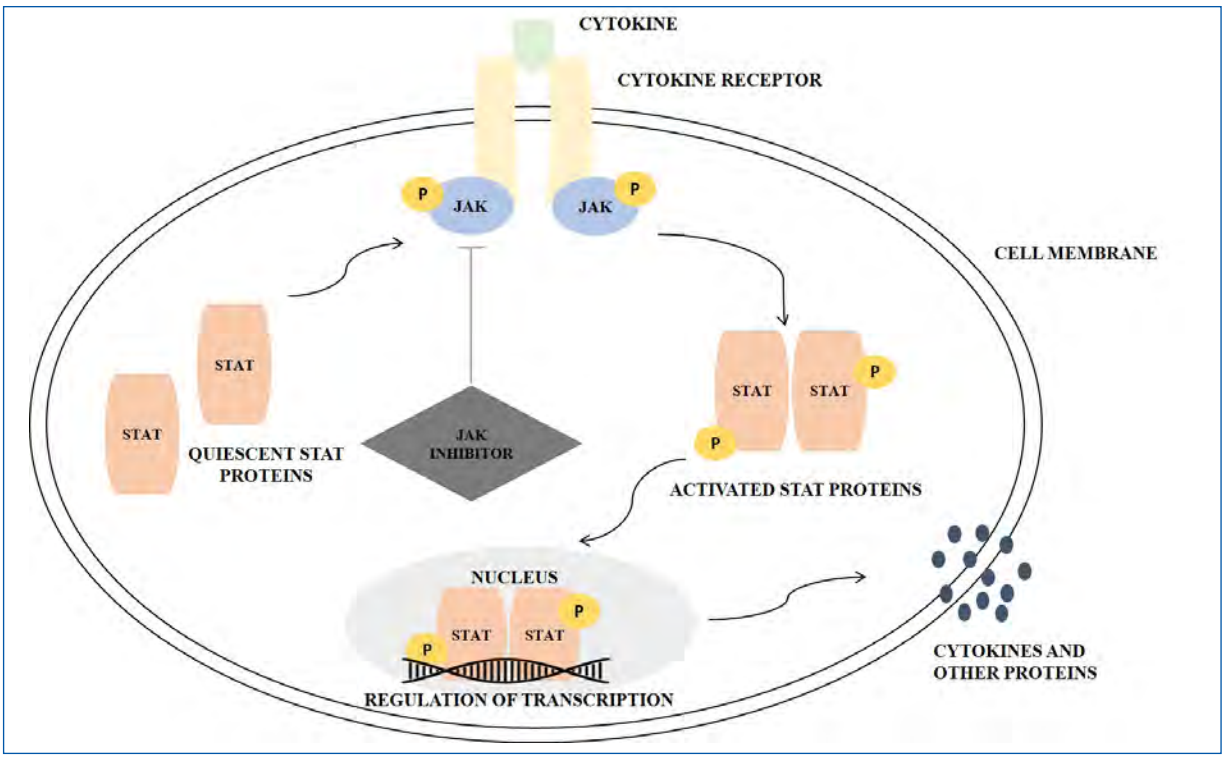

Figure 1. Schematic presentation of the JAK/STAT pathway and the role of JAK inhibition drugs. The primary function of the protein kinases is to transfer phosphate groups from adenosine triphosphate or guanosine triphosphate to the hydroxyl groups of amino acids of the protein targets. Numerous group of cytokines, such as IL-2, IL-6, IL-12, IL-21, IL-22, IL-23, and INF-ϒ interacts with type I and II cytokine receptors. Both of these receptor types lack intrinsic enzyme activity and rely on JAKs for signal transduction. After binding, recruited JAKs to initiate a signaling pathway: cytokine receptors of type I and II undergo oligomerization leading to the recruitment of JAKs, which autophosphorylate tyrosine residues. Then, STAT proteins are recruited and bind to the phosphorylated residues leading to activation mediated by phosphorylation by JAKs. Successively, the activated STAT proteins undergo dimerization enabling their translocation to the nucleus and, consequently the modulation of gene expression (*adapted from Solimani et al.*)[2].

involved in hematopoiesis. Therefore, selective inhibition of JAK1 is a desirable target to modulate a broad range of cytokines involved in the pathophysiology of AD while avoiding the effects of JAK2 inhibition, such as neutropenia and anemia[5]. A growing body of literature has demonstrated that JAK inhibitors are safe and efficacious in multiple inflammatory skin conditions, including AD[2,4].

Systemic JAK inhibitors

The first-generation inhibitor of JAK1/2, baricitinib, and JAK1 selective inhibitors, such as abrocitinib and upadacitinib were approved recently by the European Medical Agency (EMA) for the treatment of adult patients with moderate to severe AD. Upadacitinib has extended approval for children 12 years of age and older[7-9]. The approval of these systemic JAK inhibitors was a major milestone in the treatment of AD (table 1 and table 2). The safety, and efficacy with rapid relief of pruritus and clinical signs of AD explored by clinical trials (table 3) make these agents a welcome addition to the box of therapeutic options for managing AD. Currently, the monoclonal antibody dupilumab will be the main competitor. Each has its advantages, as some patients prefer a subcutaneous injection with no laboratory monitoring, whereas others may prefer the convenience of oral therapy[4]. There are no reported studies that directly compare JAK inhibitors with each other; however, a recently published network meta-analysis aimed to determine the comparative efficacy and safety of three common oral JAK inhibitors, including abrocitinib, baricitinib, and upadacitinib for moderate-to-severe AD. This network meta-analysis revealed that upadacitinib 30 mg was superior to all regimens and upadacitinib 15 mg was better than remaining regimens except for abrocitinib 200 mg in terms of Investigator's Global Assessment scale (IGA) and Eczema Area and Severity Index (EASI)

Table 1. Summary of FDA and EMA approval of JAK inhibitor drugs in dermatologic diseases and psoriatic arthritis

	Main target	EMA approval	FDA approval	Route of administration
Abrocitinib (CIBINQO®)[8,74]	JAK1	Adults with moderate-to-severe AD who are candidates for systemic therapy	Adults with refractory, moderate-to-severe AD[a]	Oral
Baricitinib (OLUMIANT®)[9,19]	JAK1, JAK2	Adults with moderate-to-severe AD who are candidates for systemic therapy; adult patients with severe AA	Adult patients with severe AA	Oral
Tofacitinib (XELJANZ®)[75,76]	Predominantly a JAK1/3 inhibitor with functional selectively over JAK2	In combination with MTX for the treatment of active psoriatic arthritis (PsA)[b]	Adult patients with active PsA with inadequate response or intolerance to methotrexate or other DMARDs	Oral
Upadacitinib (RINVOQ®)[7,77]	JAK1	Active PsA in adult patients who have responded inadequately to, or who are intolerant to one or more DMARDs[d] Treatment of moderate to severe AD in adults and adolescents 12 years and older who are candidates for systemic therapy	Adults with active PsA who have had an inadequate response or intolerance to one or more TNF blockers Adults and pediatric patients 12 years of age and older with refractory, moderate to severe AD[c]	Oral
Deucravacitinib (SOTYKTU®)[60]	TYK2	Under regulatory review for the treatment of moderate-to-severe plaque PSO	Adults with moderate-to-severe plaque PSO who are candidates for systemic therapy or phototherapy	Oral
Ruxolitinib (OPZELURA®)[39]	JAK1, JAK2	Decision agreeing on an investigation plan. Validation form EMA for a potential treatment for ≥ 12 years with nonsegmental vitiligo with facial involvement	Short-term/noncontinuous chronic treatment of mild to moderate AD in nonimmunocompromised ≥ 12 years[e] Topical treatment of nonsegmental vitiligo in ≥ 12 years	Topic

EMA: European Medical Agency; FDA: Food and Drug Administration; EU: European Union; AD: atopic dermatitis; AA: alopecia areata; DMARDs: disease-modifying antirheumatic drugs; [a]: whose disease is not adequately controlled with other systemic drug products, including biologics, or when the use of those therapies is inadvisable; [b]: in adult patients who have had an inadequate response or who have been intolerant to a prior disease-modifying antirheumatic drug (DMARD) therapy; [c]: whose disease is not adequately controlled with other systemic drug products; [d]: may be used as monotherapy or in combination with methotrexate; [e]: whose disease is not adequately controlled with topical prescription therapies.

response. Moreover, abrocitinib 200 mg was superior to abrocitinib 100 mg, and baricitinib 1, 2, and 4 mg for clinical efficacy. However, upadacitinib 30 mg caused more treatment-emergent adverse effects (AE)[10].

Topical JAK inhibitors

Topical treatments, including corticosteroids and calcineurin inhibitors, are considered standard-of-care therapy for most patients with AD; however, their clinical benefit is often limited by their anatomic use restrictions and local AEs, including skin atrophy, striae, and/or application site reactions. Long-term application of these drugs, particularly in sensitive areas, is not recommended owing to safety/tolerability. Thus, the need remains for a nonsteroidal topical therapy that is highly effective, well tolerated, and provides rapid and durable resolution of inflammatory lesions and pruritus[11].

JAK inhibitors have also been developed as a topical treatment option and are gaining attention as a treatment option for various skin diseases. Mean plasma concentrations below those achieved with the oral formulation, low incidence of AEs, and stable hematologic markers support a lack of systemic toxicity with topical JAK inhibition[12].

Delgocitinib, a first-generation pan-JAK inhibitory profile that inhibits all the JAK activities in enzyme assays, inhibits the activation of inflammatory cells, such as T cells, B cells, monocytes, and mast cells, and improves skin barrier dysfunction[13]. In a 52-week, long-term, open-label study for patients aged 16 years with mild-to-severe AD, treated with delgocitinib 0.5%

Table 2. Posology recommended for abrocitinib, baricitinib, and upadacitinib

Variables	Route of administration	Posology
Abrocitinib (CIBINQO®)[8]	Oral	The recommended starting dose is 200 mg once daily (100 mg once daily is recommended for patients ≥ 65 years of age) During treatment, the dose may be decreased or increased based on tolerability and efficacy. Maximum dose 200 mg daily
Baricitinib (OLUMIANT®)[9]	Oral	The recommended dose of baricitinib is 4 mg once daily (A dose of 2 mg once daily is appropriate for patients: aged ≥ 75 years; history of chronic or recurrent infections; sustained control of disease activity with 4 mg once daily, and are eligible for dose tapering)
Upadacitinib (RINVOQ®)[7]	Oral	≥ 18 years: The recommended dose of upadacitinib is 15 mg or 30 mg once daily based on individual patient presentation (For patients ≥ 65 years of age, the recommended dose is 15 mg once daily. The lowest effective dose for maintenance should be considered) 12-17 years: The recommended dose of upadacitinib is 15 mg once daily for adolescents weighing at least 30 kg

ointment, the proportion of patients with mEASI-50 at week 4, 24, and 52 were 31.5, 42.3, and 51.9%, respectively. While those with mEASI-75 at weeks 4, 24, and 52 were 10.9, 22.7, and 27.5%, respectively. AEs and treatment-related AEs were reported in 69.0% of the patients. The most common AE was nasopharyngitis, followed by contact dermatitis, acne, and application site folliculitis. Study discontinuations due to AEs occurred in 17 patients (3.4%), and the most common AEs leading to study discontinuation were contact dermatitis in five patients (1.0%) and application site irritation in three (0.6%)[14].

In a phase 2a study on adult patients with mild-to-moderate AD using 2% tofacitinib ointment, the mean percentage change in EASI scores from the baseline was significantly greater ($p < 0.001$) for tofacitinib (81.7%) compared to the vehicle group (29.9%) at week 4. Meanwhile, patients treated with tofacitinib ointment showed significant improvements in pruritus by day 2. Safety/local tolerability was generally similar for both treatments, although more adverse events were observed for a vehicle compared to tofacitinib[15].

Ruxolitinib (RUX) cream, a selective inhibitor of JAK1/2, demonstrated potent anti-inflammatory effects versus vehicle with rapid and sustained itch control in these phase three studies in patients with AD. Two double-blind, randomized, vehicle-controlled trials of identical design (TRuE-AD1 and TRuE-AD2) enrolled a total of 1,249 adult and pediatric subjects aged 12 and older. Patients were randomized 2:2:1 to twice-daily RUX 0.75% cream, 1.5% RUX cream, or vehicle cream for 8 continuous weeks. The primary efficacy endpoint was the proportion of subjects at week 8 achieving IGA treatment success (IGA-TS), defined as a score of 0 (clear) or 1 (almost clear) with ≥ 2-grade improvement from baseline. Efficacy was also assessed using a ≥ 4-point improvement in Itch NRS. In TRuE-AD1/TRuE-AD2 significantly more patients achieved IGA-TS with 0.75% RUX cream (50.0/39.0%) and 1.5% RUX cream (53.8/51.3%) vs vehicle (15.1/7.6%; $p < 0.0001$) at week 8. Significantly more patients in TRuE-AD1 and TRuE-AD2 achieved EASI-75 at week 8 with 0.75% RUX (56.0 and 51.5%, respectively) and 1.5% RUX (62.1 and 61.8%) vs vehicle (24.6 and 14.4%). Application site reactions were infrequent (< 1%) and lower with RUX versus vehicle. The most common treatment-related AE was application site burning sensation, which was observed primarily with vehicles (4.4%; 0.75% RUX-0.6%; 1.5% RUX-0.8%). Additionally, significant itch reductions vs vehicle were reported within 12 h of the first application of 1.5% RUX, and further reductions were observed over 8 weeks[11]. Therefore, it is thought that topical JAK inhibitors rapidly improve AD rash and symptoms relatively safely.

Currently, OPZELURA® (1.5% RUX cream) is approved in the United States (US) but not in Europe for the treatment of AD, which configurated a major milestone for the treatment of these patients. Table 1.

Alopecia areata

Alopecia areata (AA) is a chronic immune-mediated disease characterized by nonscaring hair loss with clinical heterogeneity[16]. The exact etiology of this disease is not yet elucidated, and it is thought that the hair follicle bulb immune privilege collapse is critical in the pathophysiology of the disease. Although it is not yet fully understood what causes immune privilege to collapse,

Table 3. Summary of efficacy and safety data of clinical trials of systemic JAK inhibitors approved by European Medicines Agency for the treatment of atopic dermatitis

Variables	Authors	Clinical trial	Assessment methods	Results	Safety
Abrocitinib[1]	Simpson et al.[5]	Phase 3, randomized, multicentric, double-blind, placebo-controlled trial (JADE MONO-1) 387 patients (≥ 18 years) Three groups of patients: abrocitinib 100 mg ID (n = 156), abrocitinib 200 mg ID (n = 154), placebo (n = 77)	Coprimary endpoints: Investigator Global Assessment response: score 0 (clear) or score 1 (almost clear) ≥ 75% improvement in EASI (EASI-75) score from baseline	Investigator Global Assessment response and EASI-75 at week 12: abrocitinib 100 mg ID group: 24 and 40%; abrocitinib 200 mg ID group: 44 and 63%; placebo group: 8 and 12%, respectively	AE was reported in 69% of patients in abrocitinib 100 mg ID group, 78% of patients in abrocitinib 200 mg ID group, and 57% of patients in the placebo group. Most common AE in the abrocitinib 100 and 200 mg group: nausea (n = 14, n = 31, respectively) and nasopharyngitis (n = 23, n = 18, respectively) SAE treatment-related: one patient in abrocitinib 200 mg group developed inflammatory bowel disease; one patient in abrocitinib 100 mg group developed acute pancreatitis
	Bieber et al.[78]	Phase 3, randomized, multicentric, double-blind, placebo-controlled trial (COMPARE) – 838 patients (≥ 18 years) – four groups of patients: abrocitinib 100 mg ID + topicals (n = 238), abrocitinib 200 mg ID + topicals (n = 226), dupilumab 300 mg every other week after a loading dose of 600 mg + topicals (n = 243), placebo (n = 131)	Coprimary endpoints: investigator Global Assessment response: score 0 (clear) or score 1 (almost clear) ≥ 75% improvement in EASI (EASI-75) score from baseline	Investigator Global Assessment response and EASI-75 at week 12: abrocitinib 100 mg ID group: 36.6 and 58.7%; abroctinib 200 mg ID group: 48.4% and 70.3%; dupilumab group: 36.5 and 58.1%; placebo group: 14.0 and 27.1%, respectively (all $p < 0.001$)	AE was reported in 50.8% of patients in abrocitinib 100 mg group, 61.9% of patients in the abroctinib 200 mg, 50.0% of patients in dupilumab group, and 53.4% of patients in the placebo group. The most common AE with abrocitinib was nausea, acne, nasopharyngitis, and headache SAE reported: 2.5% in abrocitinib 100 mg group, 0.9% in abrocitinib 200 mg group, 0.8% in the dupilumab group, and 3.8% in the placebo group
	Silverberg et al.[79]	– Phase 3, parallel-group randomized, multicentric, double-blind, placebo-controlled trial (JADE MONO-2) – 391 patients (≥ 18 years) – 3 groups of patients: abrocitinib 100 mg ID (n = 158), abrocitinib 200 mg ID (n = 155), placebo (n = 78)	Coprimary endpoint: Investigator Global Assessment response: score 0 (clear) or score 1 (almost clear) ≥ 75% improvement in EASI (EASI-75) score from baseline	Investigator Global Assessment response and EASI-75 at week 12: abrocitinib 100 mg ID group: 28.4% and 44.5%; abrocitinib 200 mg ID group: 38.1 and 61%; placebo group: 9.1 and 10.4%, respectively	AE was reported in 62.7% of patients in abrocitinib 100 mg ID group, 65.8% of patients in the abrocitinib 200 mg ID group, and 53.8% of patients in the placebo group Most common AE in the abrocitinib 100 and 200 mg group: nausea (n = 12, n = 22, respectively) and nasopharyngitis (n = 20, n = 12, respectively) SAE related to treatment: two in the 100 mg group (one developed pneumonia, and one developed herpangina) and two in the placebo group (one case of eczema herpeticum, and one case of staphylococcal infection). No SAE related to treatment was reported in the 200 mg group

(Continues)

Table 3. Summary of efficacy and safety data of clinical trials of systemic JAK inhibitors approved by European Medicines Agency for the treatment of atopic dermatitis *(continued)*

Variables	Authors	Clinical trial	Assessment methods	Results	Safety
	Blauvelt et al.[80]	Phase 3, randomized, multicentric, responder-enriched, double-blind, placebo-controlled trial (REGIMEN) 1,233 patients (≥ 18 years) Three periods: (a) Induction period: 12-week monotherapy with abrocitinib 200 mg ID to determine response (b) Maintenance-withdrawal period: induction period responders (IGA 0/1 response and EASI-75 response) were randomly assigned in a 1:1:1 ratio to blinded abrocitinib (200 or 100 mg ID) or placebo for 40 weeks (c) Patients with a flare during the maintenance period receive rescue treatment (abrocitinib 200 mg plus topical therapy for 12 weeks)	Primary endpoint: loss of response requiring rescue medication during the maintenance period	Of 1233 patients, 798 responders to induction (64.7%) were randomly assigned The flare probability during maintenance was 18.9, 42.6, and 80.9% with abrocitinib 200 mg, abrocitinib 100 mg, and placebo, respectively Among patients with flare in the abrocitinib 200 mg, abrocitinib 100 mg, and placebo groups, 36.6, 58.8, and 81.6% regained IGA response, respectively, and 55.0, 74.5, and 91.8% regained EASI-75 response, respectively, with rescue treatment	AE reported during maintenance was 63.2 and 54.0% of patients receiving abrocitinib 200 and 100 mg, respectively
	Shi et al.[81]	Phase 3, randomized, long extension study (JADE EXTEND) 223 patients (≥ 18 years) Patients with moderate-to-severe atopic dermatitis were randomized to receive abrocitinib 200 mg or 100 mg once daily (JADE EXTEND) after dupilumab every other week (JADE COMPARE) during 16 weeks. The final subcutaneous dose was administered at week 14 and patients received oral placebo until week 20, at which time patients were permitted to enter JADE EXTEND.	Primary endpoints: IGA, EASI and PP-NRS at baseline and at week 2, 4 and 12.	At week 12, among dupilumab responders: EASI-75 was achieved in 93.5 and 90.2% of patients who received 12 weeks of abrocitinib 200 and 100 mg, respectively PP-NRS 4-point improvement was achieved in 89,7% and 81,6%, respectively. Among patients who achieved EASI-75 but not EASI-90 with dupilumab in JADE COMPARE, 64.7% of patients treated with abrocitinib 200 mg and 54.1% of patients treated with abrocitinib 100 mg achieved EASI-90 at week 12. At week 12, among dupilumab nonresponders: EASI-75 was achieved with abrocitinib 200 mg and 100 mg in 80.0, and 67.7%. PP-NRS 4-point improvement was achieved in 77.3 and 37.8%, respectively.	– The most common treatment-emergent EA with abrocitinib 200 mg and abrocitinib 100 mg were nasopharyngitis (11.0 and 6.9%, respectively), nausea (8.2 and 0%, respectively), acne (6.8 and 2.3%, respectively) and headache (6.8 and 0.8%, respectively). SAE related to treatment: none with abrocitinib 200 mg; one patient who received abrocitinib 100 mg had eczema herpeticum.

(Continues)

Table 3. Summary of efficacy and safety data of clinical trials of systemic JAK inhibitors approved by European Medicines Agency for the treatment of atopic dermatitis *(continued)*

Variables	Authors	Clinical trial	Assessment methods	Results	Safety
Baricitinib[2]	Simpson et al.[82]	– Two independent, multicentric, double-blind, phase 3, randomized, placebo-controlled trials (BREEZE-AD1 and BREEZE-AD2). – 624 patients in BREEZE-AD1 and 615 patients in BREEZE-AD2 (≥ 18 years) – 4 groups of patients: once-daily placebo, baricitinib 1 mg, 2 mg, 4 mg in monotherapy.	Primary endpoint: – vIGA 0/1 with ≥ 2 improvement from baseline at week 16 of 4, 2 mg baricitinib and placebo	BREEZE-AD1: vIGA 0/1 response at week 16 was achieved in 16.8, 11.4, and 4.8% patients with baricitinib 4, 2, and placebo, respectively ($p < 0.001$, $p < 0.05$) BREEZE-AD2: vIGA 0/1 response at week 16 was achieved in 13.8%, 10.6%, and 4.5% patients with baricitinib 4, 2, and placebo, respectively ($p = 0.01$, $p < 0.05$)	Tretament-emergent AEs were reported in 54, 54, 58, and 58% of patients and 56, 53, 58, and 54% of patients on placebo, 1, 2, and 4 mg in BREEZE-AD1 and BREEZE-AD2, respectively Nasopharyngitis, upper-respiratory tract infections, CPK elevations and headaches were the most frequent AEs (> 2% in any group)
	Reich et al.[83]	– Phase 3, randomized, multicentric, responder-enriched, double-blind, placebo-controlled trial (BREEZE-AD7) – 329 patients (≥ 18 years) – 3 groups of patients: once-daily placebo (n = 109), baricitinib 2-mg (n = 109), 4-mg (n = 111). – All patients were on concomitant topical corticosteroids therapy and patients were permitted to use topical calcineurin inhibitors.	Primary endpoint: - vIGA 0/1 with ≥ 2 improvement from baseline at week 16 of 4mg, 2 mg baricitinib and placebo	vIGA 0/1 response at week 16 was achieved in 31, 24, and 15% of patients with baricitinib 4, 2, and placebo, respectively ($p = 0.04$ for 4 mg group and $p = 0.08$ for 2 mg group)	Tretament-emergent AEs were reported in 58, 56 and 38% of patients in baricitinib 4, 2mg, and placebo group, respectively. The most common AE were nasopharyngitis, upper-respiratory tract infections and folliculitis (≥ 2% in any group). SAE were reported in 4% in 4 mg group, 2% in 2 mg group and 4% in the placebo group.
	Silverberg et al.[84]	Phase 3, multicenter, double-blind, long-term extension study (BREEZE-AD3) 1,239 patients (≥ 18 years) Responders and partial responders (vIGA score of 0, 1 or 2) at BREEZE-AD1/BREEZE-AD2 completion remained on originally assigned treatment for 52 weeks (68 total weeks of continuous therapy).	Primary endpoint: – vIGA 0/1 at weeks 16, 36, and 52.	The proportion of baricitinib, 4 mg, responders and partial responders (n = 70) achieving or maintaining vIGA-AD (0.1) was stable: 45.7% at baseline (week 16 of continuous therapy) and 47.1% at week 68 of continuous therapy. The proportion of baricitinib, 2 mg, responders and partial responders (n = 54) achieving or maintaining vIGA-AD (0.1) was mostly stable to slightly increased (week 16, 46.3%; week 68, 59.3%).	–

(Continues)

Table 3. Summary of efficacy and safety data of clinical trials of systemic JAK inhibitors approved by European Medicines Agency for the treatment of atopic dermatitis *(continued)*

Variables	Authors	Clinical trial	Assessment methods	Results	Safety
Upadacitinib[3]	Guttman-Yassky et al.[6]	– Phase 3, randomized, multicentric, double-blind, placebo-controlled trial (Measure Up 1 and Measure Up 2) – 847 patients assigned Measure Up 1 study and 836 patients assigned Measure Up 2 study (≥ 12 years) – 3 groups of patients: • Measure Up 1: upadacitinib 15 mg (n = 281), upadacitinib 30 mg (n = 285) or placebo (n = 281) • Measure Up 2: upadacitinib 15 mg (n = 276), upadacitinib 30 mg (n = 282) or placebo (n = 278)	Coprimary endpoints: - Investigator Global Assessment response: score 0 (clear) or score 1 (almost clear) - ≥ 75% improvement in EASI (EASI-75) score from baseline	Measure Up 1: EASI-75 and vIGA 0/1 at week 16: upadacitinib 15 mg 70 and 48%; upadacitinib 30 mg 80% and 62%; placebo 16 and 8%, respectively (all $p < 0.001$). Measure Up 2: EASI-75 and vIGA 0/1 at week 16: upadacitinib 15 mg 60 and 39%; upadacitinib 30 mg 73 and 52%; placebo 13 and 5%, respectively (all $p < 0.001$).	Any treatment-emergent AE and SAE: Measure Up 1: 63 and 2% in upadacitinib 15 mg group; 73 and 3% in upadacitinib 30 mg: 59 and 3% in placebo, respectively. Measure up 2: 60 and 2% in upadacitinib 15 mg group; 61 and 3% in upadacitinib 30 mg; 53 and 3% in placebo, respectively. The most frequently reported treatment-emergent AE were acne, upper respiratory tract infection, nasopharyngitis, headache, elevation in creatinine phosphokinase and AD.
	Silverberg et al.[85]	– Phase 3, randomized, multicentric, double-blind, placebo-controlled trial (AD up) – 901 patients (> 12 years) – Three groups of patients: 300 were randomized to upadacitinib 15 mg + TCS, 297 to upadacitinib 30 mg + TCS and 340 to placebo + TCS. At week 16, a total of 283 placebo + TCS treated patients were rerandomized: 144 to upadacitinib 15 mg + TCS and 139 to upadacitinib 30 mg + TCS throught week 52	Coprimary endpoints: – Investigator Global Assessment response: score 0 (clear) or score 1 (almost clear) – ≥ 75% improvement in EASI (EASI-75) score from baseline	EASI-75 and vIGA 0/1 at week 16: upadacitinib 15 mg + TCS 64.3 and 39.3%; upadacitinib 30 mg + TCS 76.9 and 58.4%; placebo + TCS 26.3 and 1.2%, respectively EASI-75 and vIGA 0/1 at week 52: upadacitinib 15 mg + TCS 50.8 and 33.5; upadacitinib 30 mg + TCS 69.0 and 45.2%, respectively	The most frequently reported treatment emergent AE were acne, nasopharyngitis, blood creatine phosphokinase increase, dermatitis atopic and upper respiratory tract infection Rates of SAE were similar between treatment groups (8.0 and 8.1 E/100 PY with upadacitinib 15 mg + TCS and upadacitinib 30 mg + TCS, respectively

EASI-75: improvement in EASI (Eczema Area and Severity Index) score from baseline; ID: each day; AE: adverse effects; SAE: serious adverse effects; vIGA: validated Investigator Global Assessment response-defined as patients who achieved IGA 0 (clear)/1 (almost clear); PP-NRS: peak pruritus numerical rating scale; CPK: creatine phosphokinase; TCS: topical corticosteroids; E: events; PY: person-years,[1] In both monotherapy studies (MONO-1 and MONO-2) and in the combination therapy study (COMPARE), a significantly greater proportion of patients achieved at least a PP-NRS 4-point improvement (PP-NRS4 responders were patients with ≥ 4-point improvement in PP-NRS from baseline) with 100 or 200 mg once daily abrocitinib compared with placebo. This improvement was observed as early as Week 2 and persisted through Week 12. Additionally, abrocitinib significantly improved patient-reported outcomes, including itch, sleep (SCORAD Sleep VAS), AD symptoms (POEM), quality of life (DLQI) and symptoms of anxiety and depression (HADS), at 12 weeks compared to placebo[5,78,79]. In REGIMEN study, the probability of maintenance of response during 40 weeks was higher for abrocitinib 200 mg versus 100 mg and for both abrocitinib doses verus placebo. These observations support continuous abrocitinib 200 mg monotherapy as the most effective option for maintaining disease control[80,2]. In both monotherapy studies (BREEZE-AD1 and BREEZE-AD2) and in the concomitant TCS study (BREEZE-AD7), baricitinib 4 mg significantly improved patient-reported outcomes, including itch NRS, sleep (ADSS), skin pain (skin pain NRS), quality of life (DLQI) and symptoms of anxiety and depression (HADS), at 16 weeks compared to placebo[82,83,3]. The week-16 results from the Measure Up 1 and Measure Up 2 studies demonstrated that upadacitinib was superior to placebo across assessments of disease activity, itch, skin pain, and impact of AD on quality of life. Clinically and statistically significant improvements in itch were observed as early as 2 days after the first dose of upadacitinib, and skin clearance (≥ 75% improvement in Eczema Area and Severity Index [EASI-75]) was observed as early as week 2[6].

triggering factors suppress immune privilege guardian expression and locally activate the innate immune system mostly *via* CD8 + NKG2D T cells, leading to subsequent interferon-γ (IFN-γ) production and major histocompatibility complex class I upregulation that further contribute to immune privilege breakdown[16].

Current treatment options for AA, including topical, systemic, and injectable interventions, aim to immunosuppress or immunomodulate the activity of the disease, with a generally unsatisfying response and high relapse rate. Additionally, the available therapeutic options do not seem to influence the long-term course

of the disease and thus, an urgent need remains for novel, more effective therapies[16]. The nonspecific nature of these treatment modalities, along with their variable efficacy demands effort to achieve more targeted therapies that can better target the pathways involved in the disease process[17].

Local inflammation in AA is largely mediated by the JAK-STAT pathway; in this disease, there is an overexpression of proinflammatory cytokines that signal through their receptors via JAK-STAT. Additionally, this intracellular signaling network has an important role in mediating and maintaining the cytotoxic CD8 + NKG2D + T-cell reaction, which represents a driving component for AA pathogenesis. In alopecia areata, JAK1/2 and JAK1/3 lead to T-cell mediated inflammatory responses, which promote IFN-γ and IL-15 production in hair follicles and further amplify the inflammatory feedback loop[16,17]. Thus, it is not surprising that JAK inhibitors represent an emerging treatment option for AA[16,17].

There have been a number of case reports and small clinical trials reporting promising outcomes of JAK inhibitors tofacitinib, RUX, and baracitinib for alopecia areata[18]. The efficacy and safety of baricitinib were assessed in two randomized, double-blind, placebo-controlled trials (BRAVE-AA1 and BRAVE-AA2) that enrolled a total of 1200 patients with AA and led to its recent approval (2022) by the EMA and the Food and Drug Administration (FDA) (Table 1), which constituted a major milestone for the treatment of AA (Table 1)[9,19,20].

Systemic Janus Kinase inhibitors

There have been several publications of clinical research studies on the efficacy of tofacitinib (oral or topical preparation) in the treatment of AA and its variants. Liu et al. 2017, conducted a retrospective study consisting of 90 patients (aged 18-70 years) diagnosed with AA, alopecia universalis, or alopecia totalis. Patients were administered oral tofacitinib 5 or 10 mg twice daily (bid) with or without prednisolone and were evaluated using the severity of alopecia tool (SALT) scoring system at baseline and then at various treatment intervals for 4-8 months. As such, 58% of patients achieved greater than 50% change in SALT score over 4-18 months of treatment, 20% of patients were complete responders and had full regrowth with > 90% reduction in SALT, whereas 56.9% were intermediate to moderate responders (25 patients intermediate and 12 patients moderate) with 51-90% reduction in SALT for intermediate responders and 6-50% reduction in SALT for moderate responders. Additionally, 23.2% of patients were identified as nonresponders with ≤ 5% reduction in SALT[21].

Multiple case reports have examined the use of RUX in the treatment of AA. In an open-label clinical trial, Mackay-Wiggan et al. aimed to investigate RUX 20 mg orally bid in the treatment of moderate-to-severe AA. All patients received RUX for 3-6 months, followed by a 3-month observational phase to assess treatment response durability. About 9 out of 12 (75%) had significant hair regrowth and achieved the primary outcome of at least 50% regrowth, with seven of the nine responders achieving over 95% regrowth by the end of treatment[22]. The durability of responses was assessed in the 3-month follow-up period of treatment. Around three out of nine responders noted shedding beginning at week 3 following RUX discontinuation and had marked hair loss at week 12 off the drug; however, hair loss did not reach baseline levels. Around six out of nine responders reported increased shedding without major hair loss[22].

Baricitinib is now approved for the treatment of AA (Table 1)[9]. The efficacy and safety of baricitinib once daily were assessed in two randomized, double-blind, placebo-controlled trials (BRAVE-AA1 and BRAVE-AA2) that enrolled a total of 1,200 patients with AA who had at least 50% scalp hair loss as measured by the SALT for > 6 months. In both phase III 36-week studies with extension phases up to 200 weeks, patients were randomized to placebo, 2 or 4 mg baricitinib in a 2:2:3 ratio. Both trials assessed the proportion of patients who achieved at least 80% scalp hair coverage (SALT score of ≤ 20) at week 36 as the primary endpoint. Other outcomes at week 36 included the proportion of patients who achieved at least 90% scalp hair coverage (SALT score of ≤ 10), patients with Scalp Hair Assessment PRO™ score of 0 or 1 with at least a 2-point reduction on the 5-point scale, and assessments of eyebrow and eyelash hair loss. The estimated percentage of patients with a SALT score of 20 or less at week 36 was 38.8% with 4 mg baricitinib, 22.8% with 2 mg baricitinib, and 6.2% with placebo in BRAVE-AA1 and 35.9, 19.4, and 3.3%, respectively, in BRAVE-AA2. In BRAVE-AA1, the difference between 4 mg baricitinib and placebo was 32.6% points, and the difference between 2 mg baricitinib and placebo was 16.6% points ($p < 0.001$ for each dose vs placebo). In BRAVE-AA2, the corresponding values were 32.6% and 16.1% points ($p < 0.001$ for each dose vs placebo). Most patients in whom the primary outcome was met had SALT scores of 10 or less at week 36. Secondary outcomes for baricitinib at a dose of 4 mg but not at a dose of 2 mg

generally favored baricitinib over placebo[20]. In the study BRAVE-AA2, patients who had received baricitinib 4 mg once daily since the initial randomization and achieved a SALT of ≤ 20 at week 52 were rerandomized in a double-blind manner to continue 4 mg once daily or reduced dose to 2 mg once daily. The results show that 96% of the patients who remained on baricitinib 4 mg and 74% of the patients who were rerandomized to baricitinib 2 mg maintained their response at week 76[9].

Topical JAK inhibitors

Very limited studies have addressed the efficacy of topical JAK inhibitors in the treatment of AA[17]. Liu et al. in 2018 conducted an open-label, single-centre pilot study of 10 patients with AA to assess the efficacy and safety of topical tofacitinib. Patients were treated with tofacitinib 2% ointment applied bid for 6 months and were evaluated periodically for regrowth using SALT. Regrowth occurred in three patients at week 24, one patient had a SALT score percent change of 61%, while the other two patients had 18% and 25% change and seven patients had no regrowth[23]. The topical efficacy of RUX has not been well studied; there are only a few data available and the results shown are still not very encouraging[24-26].

Treatment results by route of administration and sustainability of response with JAK inhibitors

Phan et al. conducted a meta-analysis that sought to determine the expected response of AA to JAK inhibitor therapy and factors that influence response and recurrence rates. From 30 studies and 289 cases, there were 72.4% responders, 45.7% good responders, and 21.4% partial responders. The mean time to initial hair growth was 2.2 ± 6.7 months. The oral route, regardless of the specific agent of oral JAK inhibitor used in treatment, was significantly associated with four times higher odds of achieving a response when compared to topical therapy[18]. Oral JAK inhibitor treatment was also associated with seven times higher odds of achieving a good response (50-100% regrowth) than a partial response (5-50% regrowth) compared to topical treatment, with no difference between tofacitinib, RUX, or baracitinib[18]. Thus, so far, oral JAK inhibitors have demonstrated a higher efficacy in the treatment of AA than topical JAK inhibition[18].

The sustainability of treatment results with JAK inhibitors used for AA management has been a topic of concern for many researchers and clinicians[17]. In clinical practice, it has been observed that AA frequently recurs after cessation of JAK inhibitors therapy[17,18,27]. In a systemic review and meta-analysis, it has been observed that all cases of relapse were associated with cessation of therapy, on average, after 2.7 months. These results suggest that the therapeutic response may only be maintained whilst the patient is on JAK inhibitor treatment and that once ceased, relapse of AA may be expected within 3 months[18].

Vitiligo

Vitiligo is an acquired, idiopathic, and multifactorial autoimmune disorder characterized by patchy depigmentation in the skin, hair or both[28]. Depigmentation that characterizes vitiligo is caused by progressive melanocyte destruction. Activated $CXCR3^+$ $CD8^+$ T cells promote melanocyte detachment and apoptosis through INF-γ (interferon-gamma), which stimulates the JAK/STAT-1 pathway leading to the expression of INF-stimulated genes with further recruitment of $CXCR3^+$ $CD8^+$ T cells and the formation of a positive-feedback loop. The IFN-γ-chemokine axis has been identified as a potential pathway in the initiation and progression of vitiligo[28-30]. JAK inhibitors are a promising targeted treatment for vitiligo.

Systemic and topical JAK inhibitors

In vitiligo mouse models, neutralization of IFN-γ with antibody prevents $CD8^+$ T-cell accumulation and depigmentation, suggesting a therapeutic potential for this approach[29]. The JAK/STAT pathway plays a central role in vitiligo and inhibition of this intracellular signaling network has been shown to block IFN-γ signaling and contribute to repigmentation in individuals with vitiligo[31].

Tofacitinib can induce significant repigmentation in patients with vitiligo; however, concomitant stimulation of melanocytes *via* skin exposure to ultraviolet light appears to be required to achieve repigmentation[32]. Baricitinib differs from tofacitinib in that it preferentially inhibits JAK1/2 rather than JAK 3. Given IFN-γ is mediated *via* JAK1/2, it has been suggested that JAK inhibitors, which predominantly inhibit these JAKs may be more effective than others[32]. A small number of studies have addressed the efficacy of tofacitinib and baricitinib in the treatment of vitiligo (Table 4) and further research is necessary to determine their safety and efficacy.

Oral RUX interferes with IFN-γ signaling by preferential inhibition of JAK 1 and JAK 2 and has been shown

Table 4. Summary of reports with tofacitinib, baricitinib, and ruxolitinib in vitiligo

	Authors	Treatment	Patient	Results	Safety
Tofacitinib	Brittany et al.[86]	Oral tofacitinib 5 mg every other day for 1 week, then 5 mg daily	1 patient (white macules and patches involving the forehead, trunk, and extremities involving 10% of body surface area)	After 5 months, repigmentation of the forehead and hands was nearly complete, and the remaining involved areas demonstrated partial repigmentation. Approximately 5% of the total body surface area remained depigmented	No adverse effects
	Liu et al.[32]	Oral tofacitinib, 5-10 mg daily or twice daily for an average of 9.9 months	10 patients (eight patients had generalized vitiligo and two patients had primarily acral involvement, with BSA 1-10%)	A mean decrease of 5.4% BSA involvement with vitiligo was observed in five of 10 patients, at sites of either sunlight exposure or low-dose narrowband ultraviolet B phototherapy	The most common adverse event was upper respiratory infection in two patients. There were no serious adverse events.
	McKesey et al.[87]	2% tofacitinib cream twice daily in conjunction with narrowband ultraviolet B (NB-UVB) therapy twice weekly over a period of 3 ± 1 months	11 patients (the mean facial VASI was 0.80 at baseline)	The mean facial VASI was 0.23 at follow up, which is a mean improvement of 70% (range 50-87%). Mean time to follow-up was 112 days	–
	Mobasher et al.[40]	Tofacitinib 2% cream twice daily to target areas	16 patients (three patients had focal facial vitiligo, two had focal nonfacial vitiligo, while 11 had generalized vitiligo)	13 experienced repigmentation with 4 patients experiencing > 90% repigmentation; 5 patients experiencing 25-75% repigmentation; and 4 patients experiencing 5-15% repigmentation. Two patients experienced no change. Facial lesions improved more than non-facial lesions	There were no serious adverse events.
Baricitinib	Mumford et al.[88]	Oral baricitinib 4 mg daily	1 patient	At follow-up 8 months after the commencement of baricitinib, almost complete repigmentation of the hands and forearms was observed	No adverse events
	Harris et al.[31]	Oral RUX 20 mg BID	1 patient with widespread, near-complete depigmentation of his face, along with lesions on his trunk and extremities. He also had patches of nonscarring alopecia on his scalp and extremities.	At week 12: 85% scalp hair compared with 63% at baseline At week 20: improvement of facial pigmentation from 0.8% to 51% 12 weeks after discontinuing RUX, while his hair regrowth was maintained, much of the regained pigment had regressed	–

(Continues)

Table 4. Summary of reports with tofacitinib, baricitinib, and ruxolitinib in vitiligo *(continued)*

	Authors	Treatment	Patient	Results	Safety
Ruxolitinib	Rothstein et al.[41]	Topical RUX 1.5% cream BID	12 Patients with a minimum of 1% affected body surface area of vitiligo	At week 20: VASI improved 23%. Significant repigmentation (76%) in facial vitiligo in 4 patients	There were no severe or lasting side effects
	Rosmarin et al.[37,38]	1,5% RUX cream twice daily or vehicle cream twice daily (BID) for 24 weeks followed by an additional 28 weeks of treatment with 1.5% RUX cream BID for all subjects	Two double-blind, randomized, vehicle-controlled trials of identical design (TRuE-V1 and TRuE-V2) Enrolled a total of 674 adult and pediatric subjects aged 12 years and older	Primary efficacy endpoint: the proportion of subjects achieving at least 75% improvement in F-VASI (F-VASI75) at Week 24: 29.9/29.9% in RUX cream group and 7.5/12.9% in vehicle group, in TRuE-V1 and TRuE-V2, respectively Other endpoints: at week 52, approximately 50% of patients achieved F-VASI75	Treatment emergent adverse effects: 37.6/33.0% in vehicle group and 45.7/49.6% in TRuE-V1 and TRuE-V2, respectively

BID: twice daily; BSA: body surface area; F-VASI75: ≥ 75% improvement in the facial vitiligo area scoring index; VASI: vitiligo area severity index.

to improve skin conditions in some studies[28,31]. Rapid skin repigmentation on oral RUX was observed in a patient with coexistent vitiligo and AA, with marked declines in serum CXCL10 levels (chemokine ligand 10) after administration[31]. Chemokine ligand 10 (CXCL10), an IFN-γ-induced chemokine, was shown to be critical for autoreactive T-cell recruitment to the skin during the progression and maintenance of vitiligo[33,34]. However, topical administration resulted in a higher concentration in the epidermis and dermis, resulting in near-complete inhibition JAK/STAT signaling in this tissue[35]. In contrast, only partial inhibition of downstream signaling was predicted to occur after oral dosing. Therefore, dermis concentrations of RUX cream are fully effective, whereas corresponding plasma concentrations are negligible. Consequently, this distribution profile should maximize the efficacy of RUX cream in the skin while minimizing the potential for deleterious systemic effects[35]. Interestingly, according to meta-analyses, it also seems that topical JAK inhibitor formulations perform comparably to oral counterparts[36]. Two double-blind, randomized, vehicle-controlled trials (TRuE-V1 and TRuE-V2) aimed to evaluate the efficacy and safety of RUX cream for the treatment of vitiligo (Table 4). In both trials, subjects were randomized 2:1 to treatment with 1.5% RUX cream bid or vehicle cream bid for 24 weeks, followed by an additional 28 weeks of treatment with 1.5% RUX cream bid for all subjects[37,38]. Lesions on the face were assessed with the facial vitiligo area scoring index (F-VASI) and lesions on the total body (including the face) were assessed with the total body vitiligo area scoring index (T-VASI). At week 52, approximately 50% of patients achieved ≥ 75% improvement in the F-VASI75 compared to the F-VASI75 improvement from baseline reported for these patients at week 24 (the primary endpoint of the study), which was approximately 30%. Additionally, a greater proportion of patients at week 52 achieved ≥ 50% improvement in T-VASI50, and over one-third of patients achieved a vitiligo noticeability scale response. Further improvement in percentage change from baseline in facial body surface area with the application of RUX cream was also observed. RUX cream was well tolerated, the most common treatment-related TEAEs were application site acne and pruritus, no serious TEAEs were considered related to treatment and there were no significant changes in hemoglobin or platelet levels[37,38]. Based on the exciting results of TRuE-V1 and TRuE-V2, RUX was recently approved by the FDA for the topical treatment of ≥ 12 years of patients with non-segmental vitiligo (Table 1)[39].

It appears that vitiligo located on the face responds more robustly to therapy than nonfacial lesions[36,40,41]. Rothstein et al. conducted an open-label trial of bid RUX 1.5% cream in 12 patients and showed a 23% improvement in VASI scores at week 20. Four patients had significant facial involvement at baseline and had a 76% improvement in facial VASI scores[41].

Several studies have shown superior repigmentation rates in patients with JAK inhibitors and concomitant UV exposure. Joshipura et al. reported significant repigmentation in sun-exposed areas in two patients treated with

either topical RUX 1.5% bid or oral tofacitinib 5 mg bid[42]. Another retrospective case series of 10 patients treated with oral tofacitinib showed that five patients achieved some repigmentation at sites of sun exposure or UVB phototherapy[32]. Phan et al. found that a good response rate or repigmentation rate > 50% was found in 57.8% of patients treated with JAK inhibitors, but when used concurrently with phototherapy, the good response rate improved to 88.9%[36]. These data suggest that substantial repigmentation in vitiligo using JAK inhibitor may require photoactivation to stimulate melanocytes, which supports a multimodal therapeutic approach.

A few registered ongoing trials are focusing on the use of second-generation JAK inhibitors in the treatment of patients with vitiligo (https://clinicaltrials.gov/).

JAK inhibitors appear to be a promising treatment for vitiligo and the recent approval of RUX in the US was an exciting milestone for the treatment of these patients; however, further studies are required to confirm efficacy, establish safety, and investigate the durability of repigmentation.

Psoriasis vulgaris

Psoriasis (PSO) is a common chronic inflammatory skin disease with well-defined pathogenesis in which IL-23/Th17 signaling axis plays a central role. In the last years, numerous targeted treatments have been developed for PSO[2]. The majority of those affected with PSO have mild-to-moderate forms and are usually treated with topical therapy, whereas phototherapy and systemic therapies are used for those with severe disease[43]. The implication of multiple cytokines like IL-6, IL-22, IL-23, or INF-γ in PSO pathogenesis that signal through the JAK/STAT pathway suggests that the inhibition of JAKs could be a viable therapeutic option for this disease[2,43]. Additionally, recent studies have shown that PSO is mainly a JAK3 and JAK1-driven disease with a predominance of STAT3 signaling[44]. STAT3 mediates the signal of most cytokines that are involved in disease pathogenesis, including the central IL-23/IL-17/IL-22 axis, and active STAT3 is found in psoriatic skin[45,46]. Despite the recent availability of effective biological agents (monoclonal antibodies) against IL-17 and IL-23, which have radically changed the current standard of disease management, the possibility of targeting either STAT3 itself or the family of upstream activators JAKs offers additional therapeutic options[46]. Additionally, JAK inhibitors are less expensive when compared to biologics[3].

Systemic JAK inhibitors

Tofacitinib, a pan-JAK inhibitor with a predominant anti-JAK3 effect, is the most studied oral JAK inhibitor for the treatment of chronic plaque PSO[3]. Two-phase three randomized place-controlled trials (OPT Pivotal 1 and OPT Pivotal 2) demonstrated the efficacy of tofacitinib 5 or 10 mg bid over placebo in patients with moderate to severe PSO, improvement in nail PSO was also observed[47]. Nevertheless, tofacitinib 10 mg bid was more effective compared to 5 mg bid dosage[48]. Bissonnette et al. showed that continued tofacitinib worked best in PSO and that treatment discontinuation was associated with a risk of relapse; however, among relapsers, up to 60% recaptured response with tofacitinib[49]. Tofacitinib is approved by the FDA and EMA for the treatment of psoriatic arthritis, but the approval was not extended for PSO (Table 1). It is difficult to see tofacitinib achieving approval for treating PSO at the 5 mg bid dose, and there are safety concerns, as noted by the FDA, of the more effective 10 mg bid dose[48]. Numerous oral JAK inhibitors, such as abrocitinib, solcitinib, itacitinib, peficitinib, were tested for the treatment of PSO[50-53].

Tyrosine kinase (TYK2) inhibitors, such as deucravacitinib, are promising therapeutic options for the treatment of PSO, given that TYK2 is responsible for mediating immune signaling of IL-12, IL-23, and type I interferons without interfering with other critical systemic functions as other JAK proteins do[54-57]. Unlike TYK2, JAK1, 2, and 3 are responsible for mediating a series of signals that support broader systemic responses, such as hematopoiesis, myelopoiesis, lipid metabolism, and bone regulation. Consequently, JAK1, 2, and 3 inhibitors, such as tofacitinib, baricitinib, and ruxolitinib, a raised safety concerns and their clinical research in PSO have been mostly abandoned due to their unfavorable efficacy/safety ratio[58].

POETYK PSO-1 and 2 enrolled 1686 patients with moderate-to-severe PSO. After 16 weeks, in both studies, over 50% of patients treated with deucravacitinib reached PASI75, which was significantly superior to placebo and apremilast. These results were maintained through week 52, with over 65% of patients achieving PASI75 at this point in POETYK PSO-1[57,59]. A reduction in signs and symptoms was also reported by patients, with a greater impact on itch. It was well tolerated and safe[57,59].

Deucravacitinib was recently approved by the US for the treatment of patients with moderate to severe plaque PSO and had the potential to become an effi-

cacious, safe, and well-tolerated treatment (Table 1)[60]. Being an oral drug and an IL-23 inhibitor, its approval may have a great impact on clinical practice. Nevertheless, further studies are needed to evaluate long-term treatment effects.

Topical JAK inhibitors

In the past decades, the major advances in PSO therapy have been in systemic agents, such as immunomodulatory and biological molecules, while topical therapies have remained relatively unchanged[43]. It has been recently reported that psoriatic keratinocytes overexpress JAK1 and 3, making them ideal targets for topical treatment with specific JAK inhibitors[44]. However, so far, the efficacy of topical JAK inhibitors for PSO is not robust[2,3].

Tofacitinib showed interesting results as an oral agent for the treatment of PSO and topical therapy is being studied as well (Table 5). Although systemic concentrations of tofacitinib were found in patients treated with topical formulations, serologic levels were 40-fold lower than exposures from the lowest dose tested (2 mg bid) in a previous study of oral tofacitinib in patients with moderate-to-severe PSO[61].

Ruxolitinib (RUX) has been tested in topical formulations to treat mild to moderate PSO with favorable results Table 5[2,3]. Punwani et al. showed that transcriptional markers of immune cell lineage/activation in lesional skin were reduced by topical RUX, with correlations observed between clinical improvement and decreases in markers of T helper 17 lymphocyte activation, dendritic-cell activation and epidermal hyperplasia. Additionally, there was no significant inhibition of STAT3 in peripheral blood cells, suggesting limited systemic exposure[62]. In conclusion of this study, topical RUX in patients with active psoriatic lesions modulates proinflammatory cytokines[62]. Larger studies are needed to clearly establish the efficacy and safety profiles of topical RUX for the treatment of PSO, however, the data available suggest that it may be a promising agent.

Adverse effects and safety profile

JAK inhibitors that are currently approved for the autoimmune disease have an associated black warning box for the potential increased incidence of serious infections, mortality, malignancy, major adverse cardiovascular events (MACE), and thrombosis. This warning was added recently based on results from the ORAL Surveillance study of tofacitinib vs tumor necrosis factor α inhibitors (TNF inhibitors) in rheumatoid arthritis[63]. In this randomized, open-label, noninferiority, safety endpoint trial involving patients with active rheumatoid arthritis who were 50 years of age or older and had at least one additional cardiovascular risk factor, patients were randomly assigned in a 1:1:1 ratio to receive tofacitinib at a dose of 5 or 10 mg bid or a TNF inhibitor. During a median follow-up of 4.0 years, the incidences of MACE and cancer, excluding nonmelanoma skin cancer, were higher with the combined tofacitinib doses (3.4 and 4.2%, respectively) than with a TNF inhibitor (2.5 and 2.9%), the noninferiority of tofacitinib was not shown.

Safety data for tofacitinib is largely derived from clinical trials in rheumatoid arthritis and PSO, and data form RUX is from clinical trials in myelofibrosis and polycythemia vera[64].

Cohen et al., showed that the risk of infection and overall mortality in patients treated with tofacitinib is not significantly different from that observed with other biologic agents[65]. On the contrary, the ORAL Surveillance studies showed the incidence of adjudicated opportunistic infections was higher with tofacitinib than with a TNF inhibitor, however, primarily owing to the incidence of herpes zoster and all herpes zoster (nonserious and serious)[63]. JAK inhibitors are associated with an increased risk of varicella-zoster virus reactivation[63,66]. The higher rates of herpes zoster infection among patients treated with tofacitinib may be related to its mechanism of action of tofacitinib, which involves a decrease in lymphocyte activation and proliferation. Additionally, the human antiviral defense is also associated with intact responses to type I IFN and type II IFN, which receptors signal via JAK-1. Because tofacitinib inhibits signaling through JAK-1, it is possible that such a mechanism is related to an increased risk of herpes zoster infection[65]. Dose-related increases in lipid levels, such as total cholesterol, LDL cholesterol, triglycerides and HDL cholesterol, were observed in clinical trials; elevations were observed at 12 weeks and are generally mild[67,68].

Thrombosis, including deep vein thrombosis (DVT), pulmonary embolism (PE) and arterial thrombosis, has been reported in patients receiving JAK inhibitors used to treat inflammatory conditions. In the ORAL Surveillance study, higher rates of overall thrombosis, DVT, and PE were observed compared to those treated with TNF blockers[63].

Cytopenia is another potential adverse effect of JAK inhibitors, primarily JAK2 inhibition because signaling *via* JAK2 is utilized by erythropoietin, thrombopoietin, and

Table 5. Summary of reports with topical tofacitinib and ruxolitinib in psoriasis

	Authors	Clinical trial	Assessment methods	Results	Safety
Tofacitinib	Ports et al.[61]	Phase 2a study randomized, multicentric, placebo-controlled trial Adult patients with mild to moderate psoriasis (n = 71) four groups of patients: 2% tofacitinib ointment 1, vehicle 1, 2% tofacitinib ointment 2 and vehicle 2 for 4 weeks administered twice daily to a single fixed 300 cm2 treatment area containing a target plaque	Primary endpoint: percentage of change from baseline in the Target Plaque Severity Score at week 4	At week 4: Statistically significant improvement in the target plaque severity score (TPSS) for tofacitinib ointment 2% (54.4%) vs vehicle 1 (41.5%) but not for tofacitinib ointment 2% (24.2%) vs vehicle 2 (17.2%)	No serious adverse effects (AE) reported. The most common AE: nasopharyngitis and urinary tract infections
	Papp et al.[89]	Phase 2b study randomized, multicentric, vehicle -controlled trial Adult patients with mild to moderate plaque psoriasis (n = 435) groups of patients: 1% tofacitinib ointment; 2% tofacitinib ointment; vehicle applied once or twice daily	Primary endpoint: proportion of patients with Calculated Physician's Global Assessment (PGA-C) clear or almost clear and ≥ 2 grade improvement from baseline at week 8 and 12	At week 8 only significantly more patients receiving 2% tofacitinib ID and 2% tofacitinib BID achieved a PGA-C response of clear or almost clear and ≥ 2 grade improvement from baseline compared with the corresponding vehicle. Response rate was 18.6 and 8.1 for 2% tofacitinib ID and vehicle QD, respectively, and 22.5 and 11.3 for 2% tofacitinib BID and vehicle BID, respectively. At Week 12, no statistically significant differences versus vehicle were seen for 2 or 1% tofacitinib by either dosing regimen	Overall, 44.2% of patients experienced treatment-emergent AEs, 8.1% experienced application site AEs, and 2.3% experienced serious AEs. The highest incidence of AEs (including application site AEs) was in the vehicle QD group. The most frequently reported AEs were nasopharyngitis, upper respiratory tract infection and PSO
Ruxolitinib	Punwani et al.[90]	– Phase 2, double blind, and vehicle or active comparator controlled. – Adult patients with with limited (< 20% body surface area), stable but active plaque psoriasis at the baseline (n = 28) – Patients were dosed with vehicle, 0.5 or 1.0% ruxolitinib cream once a day or 1.5% twice a day for 28 days. Additional groups included two active comparators (calcipotriene 0.005% cream or betamethasone dipropionate 0.05% cream)	Improvements in lesion scores after 28 days of treatment	Although the 0.5% cream applied once a day appeared similar to the vehicle control in the response seen, the 1.0% cream applied once a day and the 1.5% cream applied twice a day both showed improvements in lesion scores greater than seen with the vehicle control. Mean total lesion score (scaling + redness + thickness) decreased by 53% after 28 days of application with 1.0% ruxolitinib cream compared with a 32% decrease in the vehicle-treated lesions (p = 0.033), whereas for 1.5% the mean lesion score decreased 54% compared with 32% for vehicle (p = 0.056)	No serious adverse effects. Local adverse effects: 20 with ruxolitinib; 28 with the vehicle; 40 with calcipotriene; 33% with betamethasone

(Continues)

Table 5. Summary of reports with topical tofacitinib and ruxolitinib in psoriasis *(continued)*

	Authors	Clinical trial	Assessment methods	Results	Safety
	Callis et al.[91]	Phase 2b vehicle-controlled study Patients with mild-to-moderate psoriasis (n = 200) Three treatment doses: 0.5, 1, and 1.5% ruxolitinib against vehicle applied daily for 12 weeks.	Reduction in PASI scores at week 12	At week 12: reduction in PASI scores was seen with different concentrations of ruxolitinib (37 with 0.5, 40 with 1, and 35 with 1.5%) compared to 20% with vehicle	No serious adverse effects.

BID: twice daily; ID: each day; PGA-C: calculated Physician's Global Assessment.

G-CSF[64]. In the treatment of bone marrow disorders with RUX, such as myelofibrosis and thrombocytopenia can be limiting[69]; however in a study of 12 patients with AA treated with RUX for up to 6 months, neither this nor other cytopenia was observed[22]. It may be theorized that patients with healthy bone marrows are less vulnerable to cytopenia observed with JAK2 inhibition[64].

In addition, respiratory infections and gastrointestinal side effects, such as nausea and diarrhea were observed[70,71]. Increased levels of transaminases, creatinine phosphokinase, and serum creatinine have also been observed; these changes have generally been graded as mild[71]. For topical applications, acne, and pruritus are often described[72].

However, the long-term safety of JAK inhibitors is still not completely understood, and as investigations of this promising drug class continue, the safety profile should become clearer. In recent years, efforts have been made to develop selective JAK inhibitors with directed targets and, consequently fewer side effects.

Possible future applications

Since the JAK/STAT signaling pathway plays a crucial role in many cytokines, a variety of inflammatory dermatological disorders may benefit from this class of immunomodulators. Currently, multiple inhibitors of the JAK/STAT pathway are being investigated for the treatment of other treatment-refractory dermatologic conditions in which activation of the JAK/STAT pathway plays a role, such as dermatomyositis, graft vs host-disease, hidradenitis suppurativa, lichen planus, lupus erythematosus, pyoderma gangrenosum, cutaneous sarcoidosis, granuloma annulare, blistering skin diseases, etc.[2,64]. The management of chronic hand eczema (CHE) remains a challenge; in a recent phase 2a trial, topical use of delgocitinib ointment resulted in clearance of CHE after 8 weeks of treatment in a significantly greater number of patients than vehicle and was well tolerated[73]. The results from this study suggest that topical delgocitinib may provide therapeutic benefits to patients with CHE with inadequate responses to topical corticosteroids[73].

Conclusion

The well-established efficacy of JAK inhibitors in inflammatory disorders, particularly rheumatoid arthritis, psoriatic arthritis, and ulcerative colitis, suggests the potential of their positive effects in a myriad of dermatological dermatoses as well. Dysregulation of the JAK/STAT pathway plays a role in the pathogenesis of many dermatologic diseases, including vitiligo, alopecia areata, PSO, and AD. JAK inhibitors can either be taken orally or have also been developed as a topical treatment option which constitutes a great advantage of this drug class. In the future, JAK inhibitors could prove to be a real alternative therapy for some inflammatory skin diseases. More studies are necessary to determine the doses that will optimize the efficacy, cost-effectiveness, and safety of this drug family for potential use in skin conditions in the long-term Table 6.

Funding

None.

Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Table 6. Key findings on JAK inhibitors in atopic dermatitis, alopecia areata, vitiligo and psoriasis vulgaris

Atopic dermatitis
Various cytokines relevant to the pathophysiology of AD activate JAK1 containing heterodimeric receptors, thereby mediating Th2 cell differentiation. Therefore, inhibition of the JAK-STAT pathway is a desirable target to modulate a broad range of cytokines involved in the pathophysiology of AD. Several oral JAK inhibitors, including abrocitinib, baricitinib, and upadacitinib, have been shown to improve the severity and symptoms of AD. In particular, an improvement in pruritus scores was detected in the early stages after the administration of these drugs. Currently, 1.5% ruxolitinib cream is approved in the United States but not in Europe for the treatment of AD, which configurated a major milestone for the treatment of these patients.
Alopecia areata
Local inflammation in AA is largely mediated by the JAK-STAT pathway; thus, it is not surprising that JAK inhibitors represent an emerging treatment option for AA. There have been a number of studies reporting promising outcomes of JAK inhibitors; the efficacy and safety of oral baricitinib led to its recent approval by EMA, which constituted an important step in the treatment of AA. To the data, oral JAK inhibitor demonstrated a higher efficacy in the treatment of AA than topical JAK inhibitor. AA frequently recurs after cessation of JAK inhibitor therapy.
Vitiligo
IFN-γ induced expression of C-X-C-motif chemokine 10 (CXCL10) in keratinocytes has been proposed as an intermediary of vitiligo depigmentation and the IFN-γ signal transduction occurs through JAK. Thus, it was postulated that JAK inhibitors may be an important therapeutic option for vitiligo by downregulating IFN-γ-chemokine axis. Topical JAK inhibitor offers a viable therapeutic alternative to topical corticosteroids and topical calcineurin inhibitors; the beneficial effects of TJK inhibitor are most pronounced on facial skin and when combined with narrowband ultraviolet B therapy. RUX 1.5% cream was recently approved by the US for the treatment of nonsegmental vitiligo.
Psoriasis vulgaris
In PSO, the involvement of JAKs has been shown and enabled the assessment of oral and topical JAK inhibitors as therapeutics. JAK1, 2, and 3 inhibitors raised safety concerns, and their clinical research in PSO has been mostly abandoned due to their unfavorable efficacy/safety ratio. Deucravacitinib is a new oral small molecule that selectively inhibits TYK2 with promising results for PSO. Although some studies have shown encouraging results with topical JAK inhibitor, their efficacy for PSO is not robust so far.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

References

1. Ciechanowicz P, Rakowska A, Sikora M, Rudnicka L. JAK-inhibitors in dermatology: current evidence and future applications. J Dermatolog Treat. 2019;30:648–58.
2. Solimani F, Meier K, Ghoreschi K. Emerging topical and systemic JAK inhibitors in dermatology. Front Immunol. 2019;10:1–19.
3. Słuczanowska-Głabowska S, Ziegler-Krawczyk A, Szumilas K, Pawlik A. Role of janus kinase inhibitors in therapy of psoriasis. J Clin Med. 2021;10:4307.
4. Nezamololama N, Fieldhouse K, Metzger K, Gooderham M. Emerging systemic JAK inhibitors in the treatment of atopic dermatitis: a review of abrocitinib, baricitinib, and upadacitinib. Drugs Context. 2020;9:1–7.
5. Simpson EL, Sinclair R, Forman S, Wollenberg A, Aschoff R, Cork M, *et al.* Efficacy and safety of abrocitinib in adults and adolescents with moderate-to-severe atopic dermatitis (JADE MONO-1): phase 3 trial. Lancet. 2020;396:255–66.
6. Guttman-yassky E, Teixeira HD, Simpson EL, Papp KA, Pangan AL, Blauvelt A, *et al.* Articles once-daily upadacitinib versus placebo in adolescents and adults with moderate-to-severe atopic dermatitis (measure up 1 and measure up 2): results from two replicate double-blind, randomised controlled phase 3 trials. Lancet. 2021;397:2151–68.
7. Summary of product characteristics - RINVOQ®.
8. *CIBINQO*. Summary of product characteristics.
9. Summary of product characteristics - OLUMIANT®.
10. Wan H, Jia H, Xia T, Zhang D. Comparative efficacy and safety of abrocitinib, baricitinib, and upadacitinib for moderate-to-severe atopic dermatitis: a network meta-analysis. Dermatol Ther. 2022;35:e15636.
11. Papp K, Szepietowski JC, Kircik L, Toth D, Eichenfield LF, Leung DYM, *et al*. Efficacy and safety of ruxolitinib cream for the treatment of atopic dermatitis: results from 2 phase 3, randomized, double-blind studies. J Am Acad Dermatol. 2021;85:863–72.
12. Hosking AM, Juhasz M, Mesinkovska NA. Topical Janus kinase inhibitors: a review of applications in dermatology. J Am Acad Dermatol. 2018;79:535–44.
13. Nakashima C, Yanagihara S, Otsuka A. Allergology International IntInnovation in the treatment of atopic dermatitis: emerging topical and oral Janus kinase inhibitors. 2022;71:40–6.
14. Nakagawa H, Nemoto O, Igarashi A, Saeki H, Murata R, Kaino H, *et al*. Long-term safety and efficacy of delgocitinib ointment, a topical janus kinase inhibitor, in adult patients with atopic dermatitis. J Dermatol. 2020;47:114–20.
15. Bissonnette R, Papp KA, Poulin Y, Gooderham M, Raman M, Mallbris L, *et al*. Topical tofacitinib for atopic dermatitis: a phase IIa randomized trial. Br J Dermatol 2016;902–11.
16. Lintzeri DA, Constantinou A, Hillmann K, Ghoreschi K, Vogt A, Blume-Peytavi U. Alopecia areata – current understanding and management. J Dtsh Dermatol Ges. 2022;20:59–90.
17. Dillon KAL. A comprehensive literature review of jak inhibitors in treatment of alopecia areata. Clin Cosmet Investig Dermatol. 2021;14:691–714.
18. Phan K, Sebaratnam DF. JAK inhibitors for alopecia areata: a systematic review and meta-analysis. J Eur Acad Dermatol Venereol. 2019;33:850–6.
19. Olumiant® (baricitinib) [prescribing information].
20. King B, Ohyama M, Kwon O, Zlotogorski A, Ko J, Mesinkovska NA, *et al*. Two phase 3 trials of baricitinib for alopecia areata. N Engl J Med. 2022;386:1687–99.
21. Liu LY, Craiglow BG, Dai F, King BA. Tofacitinib for the treatment of severe alopecia areata and variants: a study of 90 patients. J Am Acad Dermatol. 2017;76:22–8.
22. Mackay-Wiggan J, Jabbari A, Nguyen N, Cerise JE, Clark C, Ulerio G, *et al*. Oral ruxolitinib induces hair regrowth in patients with moderate-to-severe alopecia areata. JCI Insight.2016;1:e89790.
23. Liu LY, Craiglow BG, King BA. Tofacitinib 2% ointment, a topical Janus kinase inhibitor, for the treatment of alopecia areata: a pilot study of 10 patients. J Am Acad Dermatol. 2018;78:403.e1–4.
24. Bokhari L, Sinclair R. Treatment of alopecia universalis with topical Janus kinase inhibitors – a double blind, placebo, and active controlled pilot study. Int J Dermatol. 2018;57:1464–70.
25. Olsen EA, Kornacki D, Sun K, Hordinsky MK. Ruxolitinib cream for the treatment of patients with alopecia areata: a 2-part, double-blind, randomized, vehicle-controlled phase 2 study. J Am Acad Dermatol. 2019;82:412–9.
26. Deeb M, Beach RA. A case of topical ruxolitinib treatment failure in alopecia areata. J Cutan Med Surg. 2017;21:562–3.
27. Jabbari A, Sansaricq F, Cerise J, Chen JC, Bitterman A, Ulerio G, *et al*. An open-label pilot study to evaluate the efficacy of tofacitinib in moderate to severe patch-type alopecia areata, totalis, and universalis. J Invest Dermatol. 2018;138:1539–45.
28. Qi F, Liu F, Gao L. Janus kinase inhibitors in the treatment of vitiligo: a review. Front Immunol. 2021;12:790125.

29. Harris JE, Harris TH, Weninger W, Wherry EJ, Hunter CA, Turka LA. A mouse model of vitiligo with focused epidermal depigmentation requires IFN-γ for autoreactive CD8+ T-cell accumulation in the skin. J Invest Dermatol. 2012;132:1869–76.
30. You S, Cho YH, Byun JS, Shin EC. Melanocyte-specific CD8+ T cells are associated with epidermal depigmentation in a novel mouse model of vitiligo. Clin Exp Immunol. 2013;174:38–44.
31. Harris JE, Rashighi M, Nguyen N, Jabbari A, Ullerio G, Clynes R, *et al.* Rapid skin repigmentation on oral ruxolitinib in a patient with coexistent vitiligo and alopecia areata (AA). J Am Acad Dermatol. 2016;74:370–1.
32. Liu LY, Strassner JP, Refat MA, Harris JE, King BA. Repigmentation in vitiligo using the janus kinase inhibitor tofacitinib may require concomitant light exposure. J Am Acad Dermatol. 2017;77:675.e1.–82.
33. Rashighi M, Agarwal P, Richmond JM, Harris TH, Dresser K, Su M, *et al.* CXCL10 is critical for the progression and maintenance of depigmentation in a mouse model of vitiligo. Sci Transl Med. 2014;6:223ra23.
34. Searle T, Al-Niaimi F, Ali FR. Vitiligo: an update on systemic treatments. Clin Exp Dermatol. 2021;46:248–58.
35. Persaud I, Diamond S, Pan R, Burke K, Harris J, Conlin M, *et al.* Plasma pharmacokinetics and distribution of ruxolitinib into skin following oral and topical administration in minipigs. Int J Pharm. 2020;590:119889.
36. Phan K, Phan S, Shumack S, Gupta M. Repigmentation in vitiligo using janus kinase (JAK) inhibitors with phototherapy: systematic review and meta-analysis. J Dermatolog Treat. 2022;33:173–7.
37. David Rosmarin MD, *et al.* Topical ruxolitinib evaluation in vitiligo study 1 (true-v1): a phase 3, double-blind, randomized, vehicle-controlled, efficacy and safety study of ruxolitinib cream followed by an extension period in participants with vitiligo. 2022.
38. David Rosmarin MD *et al.* Topical ruxolitinib evaluation in vitiligo study 2 (true-v2): a phase 3, double-blind, randomized, vehicle-controlled, efficacy and safety study of ruxolitinib cream followed by an extension period in participants with vitiligo. In.
39. Opzelura® (Ruxolitinib) [prescribing information].
40. Mobasher P, Guerra R, Li SJ, Frangos J, Ganesan AK, Huang V. Open-label pilot study of tofacitinib 2% for the treatment of refractory vitiligo. Br J Dermatol. 2020;182:1047–9.
41. Rothstein B, Joshipura D, Saraiya A, Abdat R, Ashkar H, Turkowski Y, *et al.* Treatment of vitiligo with the topical janus kinase inhibitor ruxolitinib. J Am Acad Dermatol. 2017;76:1054.e1.–60.
42. Joshipura D, Plotnikova N, Goldminz A, Deverapalli S, Turkowski Y, Gottlieb A, *et al.* Importance of light in the treatment of vitiligo with JAK-inhibitors. J Dermatolog Treat. 2018;29:98–9.
43. Rafael A, Torres T. Topical therapy for psoriasis: a promising future. Focus on JAK and phosphodiesterase-4 inhibitors. Eur J Dermatol.2016;26:3–8.
44. Alves de Medeiros AK, Speeckaert R, Desmet E, Van Gele M, De Schepper S, Lambert J. JAK3 as an emerging target for topical treatment of inflammatory skin diseases. PLoS One. 2016;11:1–16.
45. Sano S, Chan KS, Carbajal S, Clifford J, Peavey M, Kiguchi K, *et al.* Stat3 links activated keratinocytes and immunocytes required for development of psoriasis in a novel transgenic mouse model. Nat Med. 2005;11:43–9.
46. Calautti E, Avalle L, Poli V. Psoriasis: a STAT3-centric view. Int J Mol Sci. 2018;19:171.
47. Papp KA, Menter MA, Abe M, Elewski B, Feldman SR, Gottlieb AB, *et al.* Tofacitinib, an oral Janus kinase inhibitor, for the treatment of chronic plaque psoriasis: Results from two randomized, placebo-controlled, phase III trials. Br J Dermatol. 2015;173:949–61.
48. Berekmeri A, Mahmood F, Wittmann M, Helliwell P. Tofacitinib for the treatment of psoriasis and psoriatic arthritis. Expert Rev Clin Immunol. 2018;14:719–30.
49. Bissonnette R, Iversen L, Sofen H, Griffiths CE, Foley P, Romiti R, *et al.* Tofacitinib withdrawal and retreatment in moderate-to-severe chronic plaque psoriasis: a randomized controlled trial. Br J Dermatol. 2015;172:1395–406.
50. Schmieder GJ, Draelos ZD, Pariser DM, Banfield C, Cox L, Hodge M, *et al.* Efficacy and safety of the Janus kinase 1 inhibitor PF-04965842 in patients with moderate-to-severe psoriasis: phase II, randomized, double-blind, placebo-controlled study. Br J Dermatol. 2018;179:54–62.
51. Ludbrook VJ, Hicks KJ, Hanrott KE, Patel JS, Binks MH, Wyres MR, *et al.* Investigation of selective JAK1 inhibitor GSK2586184 for the treatment of psoriasis in a randomized placebo-controlled phase IIa study. Br J Dermatol. 2016;174:985–95.
52. Bissonnette R, Luchi M, Fidelus-Gort R, Jackson S, Zhang H, Flores R, *et al.* A randomized, double-blind, placebo-controlled, dose-escalation study of the safety and efficacy of INCB039110, an oral janus kinase 1 inhibitor, in patients with stable, chronic plaque psoriasis. J Dermatolog Treat. 2016;27:332–8.
53. Papp K, Pariser D, Catlin M, Wierz G, Ball G, Akinlade B, *et al.* A phase 2a randomized, double-blind, placebo-controlled, sequential dose-escalation study to evaluate the efficacy and safety of ASP015K, a novel Janus kinase inhibitor, in patients with moderate-to-severe psoriasis. Br J Dermatol. 2015;173:767–76.
54. Papp K, Gordon K, Thaçi 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;379:1313–21.
55. Banfield C, Scaramozza M, Zhang W, Kieras E, Page KM, Fensome A, *et al.* The safety, tolerability, pharmacokinetics, and pharmacodynamics of a TYK2/JAK1 inhibitor (PF-06700841) in healthy subjects and patients with plaque psoriasis. J Clin Pharmacol. 2018;58:434–47.
56. Lé AM, Puig L, Torres T. Deucravacitinib for the treatment of psoriatic disease. Am J Clin Dermatol. 2022;23:813–22.
57. Armstrong AW, Gooderham M, Warren RB, Papp KA, Strober B, Thaçi D, *et al.* Deucravacitinib versus placebo and apremilast in moderate to severe plaque psoriasis: efficacy and safety results from the 52-week, randomized, double-blinded, placebo-controlled phase 3 POETYK PSO-1 trial. J Am Acad Dermatol. 2023;88:29–39.
58. Nogueira M, Puig L, Torres T. JAK inhibitors for treatment of psoriasis: focus on selective TYK2 inhibitors. Drugs. 2020;80:341–52.
59. Strober B, Thaçi D, Sofen H, Kircik L, Gordon KB, Foley P, *et al.* Deucravacitinib versus placebo and apremilast in moderate to severe plaque psoriasis: Efficacy and safety results from the 52-week, randomized, double-blinded, phase 3 Program fOr Evaluation of TYK2 inhibitor psoriasis second trial. J Am Acad Dermatol. 2023;88:40–51.
60. Sotyktu® (Deucravacitinib) [prescribing information]. 2022; Available from: www.fda.gov/medwatch.
61. Ports WC, Khan S, Lan S, Lamba M, Bolduc C, Bissonnette R, *et al.* A randomized phase 2a efficacy and safety trial of the topical Janus kinase inhibitor tofacitinib in the treatment of chronic plaque psoriasis. Br J Dermatol. 2013;169:137–45.
62. Punwani N, Burn T, Scherle P, Flores R, Shi J, Collier P, *et al.* Down-modulation of key inflammatory cell markers with a topical Janus kinase 1/2 inhibitor. Br J Dermatol. 2015;173:989–97.
63. Ytterberg SR, Bhatt DL, Mikuls TR, Koch GG, Fleischmann R, Rivas JL, *et al.* Cardiovascular and cancer risk with tofacitinib in rheumatoid arthritis. N Engl J Med. 2022;386:316–26.
64. Damsky W, King BA. JAK inhibitors in dermatology: the promise of a new drug class. J Am Acad Dermatol. 2017;76:736–44.
65. Cohen S, Radominski SC, Gomez-Reino JJ, Wang L, Krishnaswami S, Wood SP, *et al.* Analysis of infections and all-cause mortality in phase II, phase III, and long-term extension studies of tofacitinib in patients with rheumatoid arthritis. Arthritis Rheumatol. 2014;66:2924–37.
66. Verstovsek S, Mesa RA, Gotlib J, Levy RS, Gupta V, DiPersio JF, *et al.* Efficacy, safety, and survival with ruxolitinib in patients with myelofibrosis: Results of a median 3-year follow-up of COMFORT-I. Haematologica. 2015;100:479–88.
67. Gladman DD, Charles-Schoeman C, McInnes IB, Veale DJ, Thiers B, Nurmohamed M, *et al.* Changes in lipid levels and incidence of cardiovascular events following tofacitinib treatment in patients with psoriatic arthritis: a pooled analysis across phase iii and long-term extension studies. Arthritis Care Res (Hoboken). 2019;71:1387–95.
68. Souto A, Salgado E, Maneiro JR, Mera A, Carmona L, Gõmez-Reino JJ. Lipid profile changes in patients with chronic inflammatory arthritis treated with biologic agents and tofacitinib in randomized clinical trials: a systematic review and meta-analysis. Arthritis Rheumatol. 2015;67:117–27.
69. Galli S, McLornan D, Harrison C. Safety evaluation of ruxolitinib for treating myelofibrosis. Expert Opin Drug Saf. 2014;13:967–76.
70. Chang PH, Huang SF, Chang PS, Yu Y. Safety considerations of systemic Janus kinase inhibitors in atopic dermatitis applications. J Dermatol. 2021;48:1631–9.
71. Winthrop KL. The emerging safety profile of JAK inhibitors in rheumatic disease. Nat Rev Rheumatol. 2017;13:234–43.
72. Klein B, Treudler R, Simon JC. JAK-inhibitors in dermatology – small molecules, big impact? Overview of the mechanism of action, previous study results and potential adverse effects. J Dtsch Dermatol Ges. 2022;20:19–24.
73. Worm M, Bauer A, Elsner P, Mahler V, Molin SD, Nielsen TSS. Efficacy and safety of topical delgocitinib in patients with chronic hand eczema: data from a randomized, double-blind, vehicle-controlled phase IIa study. Br J Dermatol2020;182:1103–10.
74. Cibinqo® (abrocitinib) [prescribing information].
75. Xeljanz® (tofacitinib) [prescribing information].
76. Summary of product characteristics - XELJANZ®.
77. Rinvoq® (Upadacitinib) [prescribing information].
78. Bieber T, Simpson EL, Silverberg JI, Thaçi D, Paul C, Pink AE, *et al.* Abrocitinib versus placebo or dupilumab for atopic dermatitis. 2021;384:1101–12.
79. Silverberg JI, Simpson EL, Thyssen JP, Gooderham M, Chan G, Feeney C, *et al.* Efficacy and safety of abrocitinib in patients with moderate-to-severe atopic dermatitis: a randomized clinical trial. JAMA Dermatol. 2020;156:863–73.
80. Blauvelt A, Silverberg JI, Lynde CW, Bieber T, Eisman S, Zdybski J, *et al.* Abrocitinib induction, randomized withdrawal, and retreatment in patients with moderate-to-severe atopic dermatitis: Results from the JAK1 atopic dermatitis efficacy and safety (JADE) REGIMEN phase 3 trial. J Am Acad Dermatol. 2022;86:104–12.
81. Shi VY, Bhutani T, Fonacier L, Deleuran M, Shumack S, Valdez H, *et al.* Phase 3 efficacy and safety of abrocitinib in adults with moderate-to-severe atopic dermatitis after switching from dupilumab (JADE EXTEND). J Am Acad Dermatol. 2022;87:351–8.

82. Simpson EL, Lacour JP, Spelman L, Galimberti R, Eichenfield LF, Bissonnette R, *et al.* Baricitinib in patients with moderate-to-severe atopic dermatitis and inadequate response to topical corticosteroids: results from two randomized monotherapy phase III trials. Br J Dermatol. 2020;183:242–55.
83. Reich K, Kabashima K, Peris K, Silverberg JI, Eichenfield LF, Bieber T, *et al.* Efficacy and safety of baricitinib combined with topical corticosteroids for treatment of moderate to severe atopic dermatitis: a randomized clinical trial JAMA Dermatol. 2020;156:1333–43.
84. Silverberg JI, Simpson EL, Wollenberg A, Bissonnette R, Kabashima K, Delozier AM, *et al.* Long-term efficacy of baricitinib in adults with moderate to severe atopic dermatitis who were treatment responders or partial responders: an extension study of 2 randomized clinical trials. JAMA Dermatol. 2021;157:691–9.
85. Silverberg JI, de Bruin-Weller M, Bieber T, Soong W, Kabashima K, Costanzo A, *et al.* Upadacitinib plus topical corticosteroids in atopic dermatitis: Week 52 AD Up study results. J Allergy Clin Immunol. 2022;149:977–7.
86. Craiglow BG, King BA. Tofacitinib citrate for the treatment of vitiligo: a pathogenesis-directed therapy. JAMA Dermatol. 2015;151:1110–2.
87. McKesey J, Pandya AG. A pilot study of 2% tofacitinib cream with narrowband ultraviolet B for the treatment of facial vitiligo. J Am Acad Dermatol. 2019;81:646–8.
88. Mumford BP, Gibson A, Chong AH. Repigmentation of vitiligo with oral baricitinib. Australas J Dermatol. 2020;61:374–6.
89. Papp KA, Bissonnette R, Gooderham M, Feldman SR, Iversen L, Soung J, *et al.* Treatment of plaque psoriasis with an ointment formulation of the Janus kinase inhibitor, tofacitinib: a Phase 2b randomized clinical trial BMC Dermatol. 2016;16:15.
90. Punwani N, Scherle P, Flores R, Shi J, Liang J, Yeleswaram S, *et al.* Preliminary clinical activity of a topical JAK1/2 inhibitor in the treatment of psoriasis. J Am Dermatol. 2012;67:658–4.
91. Callis DK, Luchi M, Fidelus-Gort R. Novel mechanism for topical treatment of plaque psoriasis – results of a randomized, double blind, concentration ranging, vehicle controlled 12 week study with JAK 1/2 inhibitor INCB018424 cream. J Invest Dermatol. 2010;261.

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REVIEW ARTICLE

Pre-exposure prophylaxis (PrEP) efficacy to reduce HIV/AIDS incidence rate among male sex to male (MSM) in Asia

Eficácia da Profilaxia Pré-Exposição (PrEP) para reduzir a taxa de incidência de HIV/AIDS entre sexo masculino para homem (HSH) na Ásia

Prayogi Miura-Susanto

Faculty of Medicine and Health Sciences, Atma Jaya Catholic University, Jakarta, Indonesia

Abstract

Human immunodeficiency virus (HIV) infection is a global epidemic, with the Asia-Pacific area as the second largest contributor of cases in the world. Men sex to men (MSM) are a key population in the epidemy. One strategy to control the incidence of HIV infection is the use of pre-exposure prophylaxis (PrEP). Until now, World Health Organization (WHO) recommended two drug combinations for use PrEP containing tenofovir disoproxil fumarate and emtricitabine (TDF/FTC), which can be taken daily or as needed (on-demand). PrEP is highly effective in preventing HIV infection among the MSM group. However, the use of PrEP in Asian countries is still very low.

Keywords: Emtricitabine. HIV. MSM. PrEP. Tenofovir.

Resumo

A infeção pelo Vírus da Imunodeficiência Humana (HIV) é uma epidemia global com a região da Ásia-Pacífico como o segundo maior número de casos no mundo. O grupo de homens que fazem sexo com homens (HSH) é uma das população-chave nesta epidemia. Uma das estratégia para controlar a incidência da infeção pelo HIV é o uso da Profilaxia Pré-Exposição (PrEP). A Organização Mundial da Saúde (OMS) recomenda duas combinações de medicamentos para uso como PrEP contendo tenofovir e emtricitabina (TDF/FTC) que podem ser tomadas diariamente ou conforme necessário (sob demanda). A PrEP é altamente eficaz na prevenção da infeção pelo HIV entre o grupo HSH. No entanto, o uso de PrEP em países asiáticos ainda é muito reduzido.

Palavras-chave: Emtricitabina. HIV. HSH. PrEP. Tenofovir.

Corresponding author:
Prayogi Miura-Susanto
E-mail: prayogi.miura@yahoo.com

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Introduction

HIV was first discovered about 40 years ago, and in 2001, strategies to overcome HIV infection were launched globally by the United Nations (UN) General Assembly for the first time. However, to date HIV infection remains a global health crisis affecting all countries in the world, with 1.5 million new infections and 680,000 acquired immunodeficiency syndrome (AIDS) related deaths in 2020[1,2]. Total of 37.7 million people living with HIV in 2020, including 10.2 million who were not on HIV treatment[1]. The Asia-Pacific region is the second largest contributor, with 15% of HIV cases found in this region, including Cambodia, China, India, Indonesia, Myanmar, Nepal, Thailand, and Vietnam, which accounted for 70% of new cases across Asia in 2020[3]. Meanwhile, it was only 4.2% in the Western Europe and Central Asia regions[1,3].

The majority of people living with HIV are key populations, including men sex to men (MSM), transgender women, the person who inject drugs, sex workers, and prison inmates.[4] Globally, among key populations, homosexuals and MSM have the highest proportion of HIV infection (23 of 65%)[1]. The MSM group consists of homosexual men, bisexual men, and transgender people (male to a female)[5].

Pre-exposure prophylaxis (PrEP) is one of the strategies to prevent HIV infection, especially in populations who are at extremely high risk of acquiring HIV infection, such as MSM and transgender[6,7]. Although PrEP has been introduced for more than a decade, PrEP is still underutilized, especially in Asian countries[4]. Various factors were identified as the cause of low PrEP utilization in key populations. PrEP services have not been integrated with the existing HIV services, lack of knowledge about PrEP among key populations, and high prices are the most challenging problem in expanding the use of PrEP[3,8].

Various studies have shown the very high efficacy of PrEP to prevent HIV infection in key populations, such as MSM, and non-key populations, such as heterosexual men[9,10]. PrEP efficacy is closely related to detectable drug levels in plasma, so adherence is an important factor. PrEP has also been shown to have a good safety profile, with side effects mostly related to gastrointestinal complaints[11]. This study examines the PrEP efficacy in reducing the incidence of HIV/AIDS among MSM groups in Asian countries.

Prevalence of HIV/AIDS in Asia

HIV is part of the Retroviridae family that causes AIDS. HIV infects various cell types in the body, one of them being the surface molecule of CD4 + lymphocytes. HIV replication promotes CD4 + lymphocyte cell death. There are four stages of HIV infection that is, acute, early, chronic and late. Acute infection usually lasts for three weeks, while early infection lasts for seven weeks. Viral load indicates the risk of viral transmission and tends to be high in the acute and early phases. Long-term HIV infection causes a selective decrease in the number of CD4 + lymphocytes, resulting in an immunosuppressed condition[11].

United Nations Program on HIV and AIDS data shows a 21% decrease in new HIV infections in 2020 compared to 2010 in the Asia-Pacific region. In addition, AIDS-related deaths also decreased by 56% over the same time period. However, progress in dealing with HIV in the Asia-Pacific region is still uneven, with countries such as Thailand and Vietnam reporting a 50% reduction in infections in 2020 compared to 2010. On the other hand, Indonesia, the Philippines, and Pakistan reported an increase in HIV infections, especially in key populations such as MSM[1,4]. In addition to the significant differences between countries, the prevalence of HIV infection in Indonesia also varies between islands, where the prevalence of HIV in Java is known to be 0.5% compared to 5% in Papua[2]. As of March 2021, there were 427,201 persons living with HIV, and 131,147 people suffered from AIDS[12].

The majority of people living with HIV in the Asia-Pacific region are key populations, including homosexual men and MSM (53%), the person who inject drugs (18%), sex workers (18%), sex workers inmates, and other key populations (9%), and transgender women (2%). HIV prevalence among non-key populations in 2020 is 6%[1]. In Indonesia, HIV prevalence in the MSM group was 17.9% and became the highest among other risk groups, such as a person who inject drugs (13.7%), transgender women (11.9%), sex workers (2.1%), and prisoners (0.7%)[1,13].

HIV/AIDS infection among MSM groups

Based on UNAIDS data in 2020, MSM groups aged 15-49 accounted for an estimated 53% of new HIV infections in Asia[3]. Homosexuals and MSM are known to have a 25-fold increased risk of HIV infection compared to heterosexual men[1]. An increased risk of

HIV infection in MSM is associated with their higher numbers of sexual partners[5,14-16].

He et al., in China, found that 56.2% of study participants had more than one sexual partner[15]. Based on a study conducted in Palu, Central Sulawesi, on 90 MSM, one who had more than one sexual partner had an increased risk of HIV infection by 12.8 times compared to MSM who have only one sexual partner[16].

The higher risk of HIV infection in MSM is also caused by anal sex, which allows for rectal injury due to a lack of lubrication in the vagina. The high absorption capacity of the rectum for semen deposition also increases the risk of HIV transmission in MSM[14]. This risk increases with the lower use of condoms in anal sex[3,8]. The prevalence of unprotected anal sex in MSM with multiple partners is still very high[5,15,16]. In the United States, China, Israel, and Vietnam, the prevalence of unprotected anal sex in MSM is 11-45, 20.7, 30.3, and 51%, respectively[17]. Chen et al., in Guangzhou, China, among 204 MSM couples, 58.82% admitted to having unprotected anal sex[17]. Unprotected anal sex among MSM could increase the risk of HIV infection by 3.6 times compared to protecting one[16].

Based on the Integrated Biological and Behavioral Survey (IBBS) conducted by the Indonesian Ministry of Health in 2013, the highest HIV prevalence among MSM between 19-20% was found in Tangerang, Yogyakarta, and Makassar. The prevalence of STI (sexually transmitted infections) gonorrhea also increased in the three districts/cities from 17% in 2009 to 21% in 2013. Similar data regarding chlamydia also increased from 17 to 23%. The high prevalence of STIs and HIV among MSM in these cities may be related to the low consistency of condom use during anal sex[18]. Apart from gonorrhea and chlamydia, syphilis is also common in MSM. A meta-analysis found that the prevalence of HIV and syphilis in Indonesia is among the highest in Southeast Asia[5].

The role of PrEP in HIV/AIDS prevention

In 2015, the WHO recommended the use of oral PrEP in populations at high risk of HIV infection with an HIV incidence of more than three per 100 person-years. WHO recommends the use of PrEP containing TDF[6,7,19,20]. The PrEP regimen that was approved by the United States Food and Drug Administration (FDA) in 2012 is a tablet containing two antiretrovirals [antiretroviral drugs (ARV)], TDF (300 mg) and FTC (200 mg). In 2019, the FDA issued a permit for the use of FTC/tenofovir alafenamide (TAF) as PrEP[21-23]. In addition to TDF/FTC, lamivudine (3TC) (300 mg) can also be used as PrEP. In 2019, in addition to daily oral PrEP use, WHO added the option of using on-demand or "2 + 1 + 1" PrEP, two tablets 24 h before, one tablet 24 h after, and one tablet 48 h after sexual intercourse[3]. PrEP is now considered an important part of a combination HIV prevention program in MSM which includes the use of 100% condoms, voluntary HIV testing and counseling (volumetric computed tomography) services, and HIV treatment as prevention[6,7,24]. Currently, the administration of PrEP has been included in HIV prevention guidelines in the United States and Europe. However, it has not been done in many countries across Southeast Asia[22].

Tenofovir disoproxil fumarate (TDF) and FTC belong to the class of analog nucleoside reverse transcription inhibitors (NRTIs)[11,25]. Both TDF and FTC must be able to enter cells to then undergo phosphorylation into their active metabolites, tenofovir diphosphate, and FTC triphosphate, respectively[25]. NRTIs act intracellularly by binding directly to the nucleoside binding component. This, in turn, causes inhibition of the reverse transcriptase enzyme to form HIV deoxyribonucleic acid (DNA) from HIV ribonucleic acid. Thus, NRTIs can slow or stop viral replication in cells[11]. The clinical pharmacology of TDF and FTC depends on the intracellular half-lives of their active metabolites, where a longer half-life may decrease the frequency of drug consumption. The half-life of the TDF metabolite is about 150 h, while the FTC is about 39 h. Both are NRTI groups with the longest half-life, so they can improve patient compliance in taking medication when used as PrEP[25].

The combination of TDF and FTC as PrEP has until now been considered a practical option with a good safety and tolerability profile, cost-effectiveness, and good penetrability to targets[25]. A systematic review and a meta-analysis of 15 randomized clinical trials and three real-world observational studies showed that PrEP is safe and highly effective in reducing the risk of HIV infection[7]. The TDF/FTC combination was the first oral agent to show clinical efficacy in reducing HIV transmission in multiple randomized clinical trials. One of the disadvantages of using TDF and FTC as PrEP is their important role as a therapeutic strategy in HIV-infected patients. Thus, if the patient experiences HIV infection during PrEP, the efficacy of HIV therapy with TDF/FTC may decrease due to the presence of HIV resistance to these drugs at the time of infection[25].

After more than 1 decade since it was first introduced, PrEP use has been increasing globally. A total of 845,000 people in 54 countries received PrEP in 2020. It has increased 43% compared to 2019 and

182% compared to 2018. However, PrEP use is still concentrated in a few countries, such as the United States and other countries in East and South Africa. In addition, the current number of PrEP recipients is only 28% of the 3 million targets of PrEP recipients in low and middle incomes countries. Access to PrEP is still severely lacking in West and Central Africa, as well as Asia and the Pacific[1]. Nowadays, Australia, Thailand, and Vietnam have the highest cumulative PrEP users in Asia-Pacific[26].

Several factors affected the lack of willingness to use PrEP. These factors include lack of awareness, fear of side effects, difficulty in maintaining compliance, high costs, and societal stigma[21]. In most Asian countries, due to negative stigma, discrimination, and criminal sanctions, MSM remains a hidden population and are difficult to reach through existing HIV prevention programs[5]. The high-risk population of MSM in India, transgender women in the United States, and sex workers in Zimbabwe reported difficulties in accessing PrEP in their countries[21].

Awareness regarding the presence of PrEP is low, as shown in 93% of MSM and transgender women in India. Meanwhile, only 15.1% of sex workers in China, and 5% of homosexual men (other MSM and transgender) in Myanmar are aware of PrEP[10]. The strong stigma due to homophobia and transphobia from healthcare providers prevents key populations from accessing PrEP[5]. The success of Australia, Vietnam, and Thailand in increasing the number of PrEP users demonstrate the success of community-based strategies that can avoid stigma against key populations. Thailand launched a program entitled "Princess PrEP," in which HIV-related services are provided by trained and certified members of the key population. This ensures that HIV-related services, including the provision of PrEP, are nonjudgmental and free from stigma and discrimination. Through this program, PrEP recipients have reached 58% of the total recipients in Thailand and higher than PrEP recipients through government programs (17%) or paid programs (PrEP-15) (25%)[26].

The desire to consume PrEP is known to be quite high in key populations who already know about PrEP. A study in Wuhan, China, on 301 MSM showed that only 17% of study participants were aware of PrEP, of which 74% of study participants were willing to take PrEP if they had been given information about its effectiveness and side effects. A number of other studies have also found similar results, where the desire to consume PrEP is increased when PrEP is provided for free. In Vietnam, out of 548 MSM surveyed, only 26.8% were aware of the PrEP, but 65.7% of the participants later stated that they were willing to consume PrEP[22]. In Indonesia, PrEP has not yet been included in national regulations or programs, quite lagging far behind other emerging countries such as Thailand, which has integrated PrEP into Universal Health Coverage since 2018[8]. Apart from Thailand, Vietnam is also doing the same. Cambodia started to administer PrEP nationally in 2019[3]. PrEP is still not accessible through the national health care system and regulations regarding the availability of PrEP in Indonesia. However, PrEP can be purchased online without a prescription. However, the cost of PrEP in Indonesia is still quite high[3,8]. This relatively high price could reduce the desire of key populations to consume PrEP[8]. The estimates of PrEP users in Cambodia, Indonesia, and Myanmar were < 500 based on UNAIDS and WHO[3].

Study of PrEP efficacy in MSM groups

Based on various clinical trials, PrEP has shown an excellent efficacy and safety profile (Table 1)[9,10,20,21,27-30]. Regular use of PrEP is highly effective for preventing HIV (> 90%) and is the most effective HIV prevention currently available[21,24,31]. The efficacy of PrEP in reducing the risk of HIV transmission when combined with condom use and sex-related education ranges from 6-92%. Various studies have proven the high efficacy of PrEP in MSM[9,28,30]. High efficacy was found in the MSM population with a risk reduction rate of 44-92%. The high efficacy of PrEP in MSM is thought to be due to the better penetration of tenofovir into the anal mucosa than the vaginal mucosa[10]. Early ARV administration is known to reduce HIV transmission by 93% in non-HIV sexual partners (serodiscordant partners). Viral load suppression using PrEP has been shown to be closely associated with lower viral concentrations in genital secretions[24]. Kazemian et al., in India, estimate an increase of 0.90 life-years in MSM receiving PrEP[32].

Patient adherence to PrEP is known to be closely associated with increased PrEP efficacy.[6] The Pre-exposure Prophylaxis Initiative (iPREX) study by Grant et al., the first randomized controlled trial (RCT) of PrEP started in 2010, showed that PrEP efficacy increased by up to 92% in subjects with detectable plasma tenofovir levels. In this study, 4905 subjects from six countries were instructed to take tenofovir daily. The only Southeast Asian country that contributed to this study was Thailand (5% of the total subjects)[9,22]. Similar results were also found in the Bangkok tenofovir study, where efficacy increased from 49 to

Table 1. Study of PrEP efficacy in MSM group

Study	Methods	Subjects	Intervention	Outcomes	Results
iPrEx (2010)[9]	Randomized, placebo-controlled trial (Peru, Ecuador, South Africa, Brazil, Thailand, and the United States)	2499 HIV-seronegative MSM	1251 subjects were received TDF/FTC, 1248 subjects were received placebo. It was consumed once daily	New HIV infection, plasma drug levels, and side effects	A 44% reduction in the incidence of HIV in PrEP group (36 subjects) vs placebo (64 subjects). TDF/FTC was detected in 51% seronegative subjects vs 9% HIV-infected subjects. Nausea was reported more frequently in PrEP group vs placebo. The two groups had similar rates of serious adverse events.
TDF2 (2012)[29]	Randomized, double-blind, placebo-controlled trial (Bostwana)	1219 heterosexual adults (577 women, 642 men)	611 subjects were received TDF/FTC (331 men), and 608 subjects were received placebo (331 men)	New HIV infection, plasma drug levels, and side effects	A 62.2% reduction of HIV infection in PrEP (nine subjects) vs placebo (24 subjects). Detectable levels of plasma tenofovir and emtricitabine were found in 50% HIV-infected subjects and 80% and 81% in HIV-uninfected subjects, respectively. Nausea, vomiting, dizziness and decline in bone mineral density were more frequently in PrEP vs placebo, but the rates of serious adverse events were similar.
Partners PrEP (2012)[27]	Randomized, double-blind, three-arm, placebo-controlled trial (Kenya, Uganda)	4758 serodiscordant couple (62% HIV-1-seronegative male)	1584 randomly assigned to TDF, 1583 assigned to TDF/FTC, 1586 assigned to placebo. The drugs was consumed once daily	Adherence to therapy, new HIV infection, resistance, plasma drug levels, side effects	Treatment adherence was high (97% of dispensed study tablets were taken). The efficacies of TDF and TDF/FTC for HIV prevention in men were 63 and 84%, respectively. There was no difference in the efficacy of TDF and TDF/FTC between men and women. No participants who acquired HIV-1 after randomization were infected with an HIV-1 strain with the K65R or M184V mutation. One in the TDF group had a TDF-resistant virus K65N mutation. Tenofovir level in a plasma sample was detected in 31% seroconverted-subjects vs 82% in nonseroconverted subjects. Estimated reductions in the relative risk of acquiring HIV-1 was 86% (TDF) and 91% (TDF/FTC). There were modestly increased reports of gastrointestinal side effects and fatigue as compared with placebo but the adverse events were similar.
IPERGAY (2015)[28]	Randomized, double-blind, placebo-controlled trial (France, Canada)	414 HIV-negative MSM	206 were received TDF/FTC, 208 were received placebo. The drugs were consumed on-demand	New HIV infection, number of pills taken per month, and side effects	Relative reduction of HIV-1 infections in the PrEP group (two subjects) vs placebo (14 subjects) of 86%. Subjects took a median of 15 pills per month. There were higher rates of gastrointestinal and renal adverse events in PrEP group without any difference between two groups.
PROUD (2016)[30]	Open-label, randomized controlled-trial (United Kingdom)	544 HIV-negative MSM	275 randomly assigned to immediate group (receiving TDF/FTC at the enrollment visit), 269 assigned to deferred group(receiving TDF/FTC after a deferral period of 1 year)	New HIV infection, drug side effects, compensation risk	The incidence of HIV-infections in immediate group was lower (three subjects) than deferred group (20 subjects) with absolute difference of 7.8/100 person years. 13 men in a similar population would need access to 1 year of PrEP to avert one HIV infection. No adverse events between two groups. No difference in the occurrence of sexually transmitted infections between groups which shows no compensation risk.

74% in subjects with detectable plasma tenofovir levels[10]. In the TDF2 study, tenofovir and FTC were detected in 80% of nonseroconverters compared to seroconverters (50%)[25]. Detection of tenofovir in plasma was associated with regular tenofovir consumption[11,22].

Adherence to PrEP could be associated with PrEP-related knowledge and self-perceived level of risk of acquiring HIV. Cempaka et al. study in Bali, including 220 MSM and transgender, showed an increase in the desire to take PrEP occurred after study participants

were provided with information about the benefits of PrEP, especially in high-risk participants who had more than one sexual partner and did not use condoms consistently[8].

To date, the recommended regimen was daily PrEP consumption for high-risk populations. However, a number of studies have shown that on-demand PrEP use could also achieve similar effectiveness to daily consumption. The Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD) study by McCormack et al., in 544 high-risk MSM who had unprotected anal sex (29 Asian) showed that in a setting close to real-world conditions, regular daily consumption of PrEP could provide higher protection against HIV infection in populations-at-risk than MSM who had not taken PrEP[22,30]. The on-demand Antiretroviral pre-exposure prophylaxis for HIV infection in men who have sex with men (IPERGAY) study using an on-demand PrEP regimen also showed similar results. Study participants only took two tablets of TDF/FTC 24 h before sex, one tablet 24 h after sex, and one tablet 48 h after sex. The results of the study showed that there was a decrease in the incidence of HIV by 86%, with a median 16 tablets consumed per month. This regimen requires lower costs, improves adherence, and facilitates discontinuation of consumption when the patient is no longer exposed to high-risk[22,28].

The basis of the on-demand regimen is the knowledge about the concentration of the HIV virus in the vaginal or anal mucosa after sexual activity. The study found that HIV was concentrated in the peri-cervical region and the rectosigmoid colon for 24 h after sexual activity. Thus, optimal administration of PrEP should be able to ensure adequate concentrations of ARVs in the peri-cervical and rectosigmoid areas before and 24 h after sexual activity[25]. Thus, the main key to reaching PrEP effectivity in preventing HIV infection is to maintain therapeutic levels of plasma drugs either through daily consumption regimens or on-demand-based regimens. Both regimens have their respective drawbacks. Daily regimens can reduce the desire to take PrEP. On the contrary, on-demand regimens will be difficult to implement for those who frequently engage in unplanned sex[22].

The combination of TDF/FTC is known to have better efficacy than monotherapy with TDF[10]. The results of RCT conducted in Kenya and Uganda involving 4,747 serodiscordant HIV partners showed that TDF/FTC PrEP reduced the risk of infection by 73%, while monotherapy with TDF alone showed a 62% reduced risk of infection[33]. A study on levels of tenofovir-diphosphate and FTC triphosphate, the active metabolites of TDF and FTC, found that a third daily dose of TDF/FTC created a protective mucosal layer in 98% of subjects. However, this must be supported by sufficient adherence, where 85 and 28% compliance is required to obtain the protective effect in women and men subjects, respectively. Thus, the TDF/FTC combination is considered to be more effective in men than women[11].

The combination of TDF/FTC as PrEP can also reduce acute plasma viremia in HIV-infected experimental animals and successfully minimize acute viral replication. However, the effect of TDF/FTC on cell-associated DNA levels was only temporary. Thus, in people with suboptimal PrEP levels and infected with HIV, the effect of PrEP is not able to reduce the number of HIV-infected cells in the body. Besides, PrEP can also prevent STIs that can increase the risk of HIV infection. A study investigated the effect of TDF/FTC consumption in the MSM group on herpes simplex virus (HSV)-2 infection. It showed that TDF/FTC could reduce the incidence of ulcers due to HSV-2 infection but not the acquisition of HSV-2 infection in MSM. Another study in a heterosexual population found that daily oral intake of PrEP TDF/FTC may reduce the risk of HSV-2 infection. This suggests additional benefits of taking PrEP for populations at risk[11].

The implementation of PrEP had a direct impact on health and economic aspect. Ten Brink et al. used data from eight countries in Asia (Cambodia, China, India, Indonesia, Myanmar, Nepal, Thailand, and Vietnam) to find that if the implementation of PrEP among MSM in 2022 could be increased and expanded, there will be an increase in the coverage of PrEP use by 15% among MSM at the end of 2026, prevention of 100,000 cases of HIV infection and 300,000 DALYs in 2022-2031. This could also save the cumulative cost of providing ARVs for 5 years of therapy as much as 12.3 million USD[3]. Similar results were previously stated by Suraratdecha et al., where giving PrEP to high-risk MSM is a cost-effective strategy[20].

The use of PrEP generally showed a good tolerable profile. Most PrEP side effects are related to gastrointestinal complaints such as vomiting, loose stools, and diarrhea. Only 1.0-18.5% of patients experienced these side effects[10]. A mild decrease in bone density can be found mainly in the spine[10,11,29]. Decreased bone density in young male patients after PrEP consumption is thought to be caused by an endocrine disorder, parathyroid hormone-vitamin D-fibroblast

growth factor 23. The decrease in bone mineral density due to PrEP consumption is considered insignificant compared to the success of TDF in preventing HIV infection[11]. The development of new tenofovir preparations, such as TAF is expected to further reduce side effects and increase PrEP tolerability. Further studies are needed to assess the long-term side effects of using PrEP[10].

Tubulopathy (proximal tubular dysfunction) is one of the TDF side effects. However, studies have shown that daily oral PrEP TDF/FTC consumption is not associated with tubulopathy within 24 months of PrEP consumption[34]. Another study found that PrEP may cause subclinical tubular dysfunction characterized by increased urinary a1-microglobulin (a1m) levels and proteinuria[35]. A randomized clinical trial found a minimal and nonprogressive decrease in the estimated glomerular filtration rate (eGFR) due to TDF/FTC consumption for 18-36 months in the heterosexual HIV-1-uninfected population. The decrease in mean eGFR is known to be reversible a few weeks after the discontinuation of PrEP consumption. However, a meta-analysis showed an increased risk of renal failure with daily oral TDF/FTC consumption, as indicated by an increase in serum creatinine levels[11].

Conclusion

HIV infection is still a major global health crisis, especially regarding key populations, such as MSM. PrEP is an HIV prevention option for people who are at high risk of HIV infection. The effectiveness of PrEP in preventing HIV infection has been shown to be very high, especially in combination with other preventive methods. In addition, the WHO recommendation on PrEP (TDF/FTC) has a good safety profile. Related to the diversity of social and cultural backgrounds in Asian countries, further studies on the implementation of PrEP are required to determine its efficacy in reducing the incidence of the HIV epidemic in this region.

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Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

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References

1. UNAIDS. UNAIDS data 2021 [Internet]. 2021 [cited 2022 June 19]. Available from: https://www.unaids.org/sites/default/files/media_asset/JC3032_AIDS_Data_book_2021_En.pdf
2. Challacombe SJ. Global inequalities in HIV infection. Oral Dis. 2020;26:16–21.
3. TenBrink DC, Martin-Hughes R, Minnery ME, Osborne AJ, Schmidt HMA, Dalal S, *et al*. Cost-effectiveness and impact of pre-exposure prophylaxis to prevent HIV among men who have sex with men in Asia: a modelling study. PLOS ONE. 2022;17:1–13.
4. Green K, Schmidt HMA, Vallely AJ, Zhang L, Kelly-Hanku A, Janamnuaysook R, *et al*. Ending AIDS in the Asia-Pacific region by 2030: are we on track? Policy, epidemiological and intervention insights. Sexual Health. 2021;18:31–40.
5. Mahmud S, Mohsin M, Muyeed A, Hossain S, Mynul Islam M, Islam A. Prevalence of HIV and syphilis and their co-infection among men having sex with men in Asia: a systematic review and meta-analysis. medRxiv. 2021:1–31.
6. Hillis A, Germain J, Hope V, McVeigh J, Van Hout MC. Pre-exposure prophylaxis (PrEP) for HIV prevention among men who have sex with men (MSM): a scoping review on PrEP service delivery and programming. AIDS and Behavior. 2020;24:3056–70.
7. Zhang L, Peng P, Wu Y, Ma X, Soe NN, Huang X, *et al*. Modelling the epidemiological impact and cost-effectiveness of PrEP for HIV transmission in MSM in China. AIDS and Behavior. 2019;23:523–33.
8. Cempaka R, Wardhani B, Sawitri AAS, Januraga PP, Bavinton B. PrEP use awareness and interest cascade among MSM and transgender women living in Bali, Indonesia. Trop Med Infect Dis. 2020;5:1–12.
9. Grant RM, Lama JR, Anderson PL, McMahan V, Liu AY, Vargas L, *et al*. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men.N Engl J Med. 2010;363:2587–99.
10. Spinner CD, Boesecke C, Zink A, Jessen H, Stellbrink HJ, Rockstroh JK, *et al*. HIV pre-exposure prophylaxis (PrEP): a review of current knowledge of oral systemic HIV PrEP in human. Infection. 2016;44:151–8.
11. Yap PK, Loo Xin GL, Tan YY, Chellian J, Gupta G, Liew YK, *et al*. Antiretroviral agents in pre-exposure prophylaxis: emerging and advanced trends in HIV prevention. J Pharm Pharmacol. 2019;71:1339–52.
12. Kementrian Kesehatan Republik Indonesia. Perkembangan HIV. AIDS dan penyakit infeksi menular seksual (PIMS) Triwulan I Tahun 2021 [Internet]. 2021. [cited 2022 June 19]. Available from: https://www.google.com/search?q=PIMS+TW+1+2021.&oq=pims&aqs=chrome.0.69i59j69i57j46i512j0i512l2j46i175i199i512j0i512l4.1081j0j7&sourceid=chrome&ie=UTF-8
13. Kementrian Kesehatan Republik Indonesia. InfoDATIN HIV. AIDS [Internet]. 2020. [cited 2022 June 19]. Available from: https://pusdatin.kemkes.go.id/resources/download/pusdatin/infodatin/infodatin-2020-HIV.pdf
14. Fatmala DR. Faktor predisposing, enabling, dan reinforcing dalam pemanfaatan VCT oleh laki-laki seks dengan laki-laki (LSL). Jurnal Berkala Epidemiologi. 2016;4:138–50.
15. He J, Xu HF, Cheng WB, Zhang SJ, Gu J, Hao YT, *et al*. Intimate relationship characteristics as determinants of HIV risk among men who have sex with regular male sex partners: a cross-sectional study in Guangzhou, China. BMC Infect Dis. 2018;18:1–12.
16. Maharani J, Seweng A, Sabir M, Tahir M, Stang, Indar, *et al*. Sexual behavior influence against HIV/AIDS in homosexuals at Palu City in 2020. Gaceta Sanitaria. 2021;35:135–9.
17. Chen S, Yang Q, He J, Fan X, Liu Z, Qiu J, *et al*. The effects of intimate relationship characteristics on unprotected anal intercourse among same-sex male couples in China: a dyadic analysis using the actor-partner interdependence model. BMC Infect Dis. 2021;21:1–12.

18. Kementrian Kesehatan Republik Indonesia. Rencana aksi kegiatan (RAK) Tahun 2015-2019 Revisi Kesatu [Internet]. 2019. [cited 2022 June 22]. Available from: https://e-renggar.kemkes.go.id/file2018/e-performance/1-415780-4tahunan-029.pdf.
19. World Health Organization. Appropriate medicines: options for pre-exposure prophylaxis [Internet]. 2016. [cited 2022 June 19]. Available from: https://apps.who.int/iris/bitstream/handle/10665/273934/WHO-CDS-HIV-18.22–eng.pdf.
20. Suraratdecha C, Stuart RM, Manopaiboon C, Green D, Lertpiriyasuwat C, Wilson DP, *et al*. Cost and cost-effectiveness analysis of pre-exposure prophylaxis among men who have sex with men in two hospitals in Thailand. J Int AIDS Soc. 2018;21:1–8.
21. Lau JY, Hung CT, Lee SS. A review of HIV pre-exposure prophylaxis (PrEP) programmes by delivery models in the Asia-Pacific through the healthcare accessibility framework. J Int AIDS Soc. 2020;23:1–14.
22. To KW, Lee SS. HIV pre-exposure prophylaxis in South East Asia: a focused review on present situation. Int J Infect Dis. 2018;77:113–7.
23. Kamitani E, Johnson WD, Wichser ME, Adegbite AH, Mullins MM, Sipe TA. Growth in proportion and disparities of HIV PrEP use among key populations identified in the United States National Goals: systematic review and meta-analysis of published surveys. J Acquir Immune Defic Syndr. 2020;84:379–86.
24. Kementerian Kesehatan Republik Indonesia. Keputusan Menteri Kesehatan Republik Indonesia pedoman nasional pelayanan kedokteran tata laksana HIV [Internet]. 2019. [cited 2022 June 19]. Available from: https://yankes.kemkes.go.id/view_unduhan/46/kmk-no-hk0107menkes902019.
25. Blumenthal J, Haubrich R. Pre-exposure prophylaxis for HIV infection: how antiretroviral pharmacology helps to monitor and improve adherence. Exp Opin Pharmac. 2013;14:1777–85.
26. Janamnuaysook R, Green KE, Seekaew P, Ngoc Vu B, Van Ngo H, Anh Doan H, *et al*. Demedicalisation of HIV interventions to end HIV in the Asia-Pacific.Sexual Health. 2021;18:13–20.
27. Baeten JM, Donnell D, Ndase P, Mugo NR, Campbell JD, Wangisi J, *et al*. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. N Engl J Med. 2012;367:399–410.
28. Molina JM, Capitant C, Spire B, Pialoux G, Cotte L, Charreau I, *et al*. On-demand preexposure prophylaxis in men at high risk for HIV-1 infection. N Engl J Med. 2015;373:2237–46.
29. Thigpen MC, Kebaabetswe PM, Paxton LA, Smith DK, Rose CE, Segolodi TM, *et al*. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. N Engl J Med. 2012;367:423–34.
30. McCormack S, Dunn DT, Desai M, Dolling DI, Gafos M, Gilson R, *et al*. Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial. Lancet. 2016;387:53–60.
31. O'Leary A, DiNenno E, Honeycutt A, Allaire B, Neuwahl S, Hicks K, *et al*. Contribution of anal sex to HIV prevalence among heterosexuals: a modeling analysis. AIDS and Behavior. 2017;21:2895–903.
32. Kazemian P, Costantini S, Kumarasamy N, Paltiel AD, Mayer KH, Chandhiok N, *et al*. The cost-effectiveness of human immunodeficiency virus (HIV) preexposure prophylaxis and HIV testing strategies in high-risk groups in India. Clin Infect Dis. 2020;70:633–42.
33. Kadek N, Purnamayanti D, Yuni N, Usemahu P, Haris F, Layun MK, *et al*. Strategi monitoring kepatuhan penggunaan antiretroviral pre-exposure prophilaxis pada pasangan serodiscordant. Berita Kedokteran Masyarakat. 2019;35:1–6.
34. Mugwanya K, Baeten JM, Celum C, Donnell D, Nickolas T, Mugo N, *et al*. Low risk of proximal tubular dysfunction associated with emtricitabine-tenofovir disoproxil fumarate preexposure prophylaxis in men and women. J Infect Dis. 2016;214:1050–7.
35. Jotwani V, Scherzer R, Glidden DV, Mehrotra M, Defechereux P, Liu A, *et al*. Pre-exposure prophylaxis with tenofovir disoproxil fumarate/emtricitabine and kidney tubular dysfunction in HIV-uninfected individuals. J Acquir Immune Def Syndr. 2018;78:169–74.

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REVIEW ARTICLE

Imported sexually transmitted infections in Europe

Infeções sexualmente transmissíveis importadas na Europa

Diogo de Sousa[1,a] and João Borges-Costa[1,2,3]*

[1]Dermatology Department, Hospital de Santa Maria, Centro Hospitalar Universitário Lisboa Norte; [2]Dermatology Universitary Clinic, Faculdade de Medicina da Universidade de Lisboa; [3]Institute of Hygiene and Tropical Medicine, Universidade Nova de Lisboa. Lisbon, Portugal

[a]ORCID: 0000-0002-5415-887X

Abstract

Over the last century, the world experienced the impact of population movements on infectious diseases. Sexually transmitted infections (STI) remain a major public health problem with a significant burden worldwide. Several factors influence the incidence, distribution, and types of STIs, including the increasing travel abroad. Foreign travel is in many ways related to the spread of diseases, and with the increasing affordability of air travel, there is a risk of the rapid globalization of emerging infections. History shows that this phenomenon is not new and Europe has many examples of imported STIs, such as syphilis and *Lymphogranuloma venereum* (LGV). STIs acquired during international travel are more likely resistant to standard antimicrobials, thus helping onward transmission of drug-resistant strains, such as in *Neisseria gonorrhea* infections. As we move to an era where travel and migration are more accessible than ever before, we are expected to face new challenges when it comes to infectious diseases-and STIs are no different. Because pathogens know no borders, the world needs to move cohesively and swiftly to provide an effective response. Clinical care services must be expanded and strengthened, working in web-based systems to ensure that new pathogens are readily identified and targeted, safeguarding populations' health.

Keywords: Drug resistance. Epidemiology. Immigration. Sexually transmitted diseases. Travel.

Resumo

Ao longo do último século o ficou visível o impacto que os movimentos das populações podem ter nas doenças infeciosas. As infeções sexualmente transmissíveis (IST) são ainda um problema de saúde pública prioritário, com importante impacto globalmente. Vários fatores influenciam a incidência, distribuição e tipos de IST, incluindo as crescentes viagens internacionais. A disseminação de doenças está intrinsecamente relacionada com os movimentos das populações e com a crescente disponibilidade de viagens aéreas, o risco de uma rápida globalização de infeções emergentes. Este fenómeno não é novo, tendo a Europa vários exemplos de IST importadas na sua hisória, como a síflis e o *Lymphogranuloma venereum*. As IST adquiridas em viagens internacionais são mais frequentemente resistentes a antimicrobianos de primeira linha, contribuindo para a disseminação de estirpes resistentes, como a a infeção por *Neisseria gonorrhea*. À medida que as viagens e as migrações estão cada vez mais acessíveis, é expectável o aparecimento de novos desafios com a difusão de doenças

***Corresponding author:**
Diogo de Sousa
E-mail: 27949@chln.min-saude.pt

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infeciosase as IST não serão diferentes. Como os agentes infeciosos não estão limitados por fronteiras, as medidas para gerir estes desafios devem ser coesas e céleres, em todo o globo. Os agentes de saúde devem ser expandidos e reforçados, atuar em sistemas em rede para assegurar que novos agentes patogénicos são rapidamente identificados e mitigados, preservando a saúde das populações.

Palavras-chave: Epidemiologia. Imigração. Infeções sexualmente transmissíveis. Resistências antibióticas. Turismo.

Introduction

Sexually transmitted infections (STI) remain a major public health problem with an important burden worldwide. The World Health Organization (WHO) estimates that around 340 million people live with STIs worldwide every year. A health issue that recently led WHO to establish key strategic and operational transformations required to end STIs as public health concern by 2030[1].

Early in the 20th century, in response to the dramatic increase in the number of people with STIs against an economic crisis, genitourinary medicine emerged in Great Britain, aiming to provide healthcare to all facets of sexual health. Over time, people and their sexual behavior have changed, and so have STIs.[2] Several factors influence the incidence, distribution, and types of STIs, including the consistently increasing travel abroad and population migration[3,4]. Foreign travel is in many ways related to the spread of diseases, and with the increasing affordability of air travel, there is a risk of the rapid globalization of emerging infections[3]. Immigration to Europe has also been identified as a health priority issue in Europe, as refugees, asylum seekers, and irregular migrants are particularly vulnerable to infectious diseases and may have worse health outcomes than the host population[4].

Historical trends suggest that this phenomenon is not new and has had devastating consequences in certain populations. For instance, syphilis is believed to have been taken into Europe by explorers, and the globalization of human immunodeficiency virus (HIV) has also been helped by travel and migration[5]. Many reasons make foreign travel a risk factor for the acquisition of STIs. When abroad, people may feel less inhibited due to a perceived relaxation of social and moral constraints, leading to changing sexual behavior and exposure to STIs, with an estimated 20% of travelers having sex with new partners[3]. STIs acquired during international travel are more likely to be resistant to standard antimicrobial regimens, with the risk of higher sexual exposure and an increased chance that treatment regimens abroad may not be efficient in the local population, thus helping onward transmission of drug-resistant strains, such as *Neisseria gonorrhea* in Asia[6].

In Europe, the increased migration flux heightens the chances of importing infections as migrants from different geographic areas may have higher incidence rates of STIs like hepatitis B and C and recombinant forms of HIV with drug-resistant profiles[7]. A total of > 30 million of Europe's inhabitants have an immigration background, of which approximately one-third were born outside industrialized countries-regions with a different infectious diseases profile seen in Europe[7].

The purpose of this review is to compile data from studies spanning Europe and dealing with some of the most impactful and rising imported STIs. The resulting overview of key STIs affecting migrant populations in Europe reflects the present state of knowledge in this field and may serve as a guide for planning public health policies and as an appeal for further research and prevention.

Syphilis

The bacterium responsible for syphilis is *Treponema pallidum (T. pallidum)* subsp. *pallidum*. Other names used for syphilis in the past include lues and the French disease, or hard chancre for primary syphilis. In recent years, syphilis has experienced a renaissance-like virtually no other STI[8].

Two main hypotheses are proposed to describe the emergence of syphilis in Europe. The precolumbian hypothesis advocates that treponemal diseases have always had a global distribution[9]. In Europe, most of these conditions were mistaken for leprosy[10]. According to this theory, both syphilis and non-venereal treponemal diseases are variants of the same infections, and the clinical differences are the consequence of geographic and climate deviations and the degree of cultural and social development of populations within distinct areas. Briefly, pinta, yaws, endemic syphilis, and venereal syphilis are considered adaptative responses of *Treponema* to changes in the environment, cultural differences, and contact between various populations[10,11]. Yaws, endemic in Africa around 10,000 BC, would have remained unmodified in countries with similar climate conditions as those in the origin countries but would have developed into endemic syphilis in

Table 1. First report dates of STIs in Europe

STI	Date of the first report in Europe
Syphilis	1493[9]*
HIV	1985[16]
LGV	1989[22]
Zika	2013[29]
MPX	2022[41]**

*According to the Columbian hypothesis.
**Date of sustained local transmission; there are sporadic reports of MPX infection in Europe previous to 2022. HIV: human immunodeficiency virus; LGV: lymphogranuloma venereum; STI: sexually transmitted infection.

countries with colder and drier climates in which personal hygiene was overlooked and disregarded or into venereal syphilis in those areas where inhabitants exhibited a civilized society and paid more attention to personal hygiene[9].

The Columbian hypothesis is a popular theory stating that the navigators in Columbus's fleet would have brought the infection on their return from the New World around 1493 (Table 1)[9,12]. This theory is supported by documents belonging to Spanish physicians who were present at the moment when Christopher Columbus returned from America, who had already described the disease in some crew members on their return from the New World[9]. Further experiments have supported this hypothesis by finding evidence consisting of specific lesions on skeletal remains, such as luetic lesions, dated after Columbus's journey in America[13].

At the very beginning in Europe, syphilis was a disease of great severity and atypical evolution as compared to nowadays syphilis, with no rare fatal case[9]. The supporters of the Columbian hypothesis advocate that the severity of the condition was mainly due to its novelty, as the population had no time to gain immunity against the illness when venereal syphilis became endemic in Europe, certain strains of *T. pallidum* were selected, and the disease gained a milder course[9]. The hallmark of ancient syphilis probably is *tabes dorsalis*, the late neurological complications of syphilis, nowadays almost extinct[14]. Lues maligna, a rare form of ulceronodular secondary syphilis, is probably the presentation most similar to the first cases seen in Europe seen nowadays, mostly in immunocompromised patients (Figure 1)[15].

Today, Europe is far from free from the syphilis epidemics, with the resurgence of syphilis over the last decades in high-income countries of the European Union and the European Economic Area (EU/EEA)[8]. For instance, the number of cases reported among men who have sex with men (MSM) in the EU/EEA has more than doubled (164% increase) from 2010 to 2016[8], thus supporting the need for public health programs that not only scout for emerging infections but also manage to know pathogens with an impactful burden.

HIV infection

In the 20th century, almost 500 years after the arrival of syphilis, the first cases of HIV in Europe were observed in 1985 (Table 1)[16].

Human immunodeficiency virus (HIV) epidemiology in Europe is influenced by migration[17]. The epidemiology of migration-associated HIV reflects the disease in the migrants' native countries. This relationship manifests in the transmission patterns and differences in the demographics and biometrics of the populations at risk[16]. European reports show that in 2015, for instance, 37% of all newly-diagnosed cases of HIV in the EU/EEA were in people born outside of the reporting country[18]. Low rates of testing and high rates of late diagnosis reflect gaps in HIV testing services for migrants as well as barriers to the provision and uptake of HIV testing services in this population[18].

One of the most significant impacts of immigration on the HIV epidemic is the implication in the molecular epidemiology of the virus. Different features of HIV-1 molecular epidemiology, especially for the distribution of viral subtypes and for transmission of drug-resistant profiles, have been associated with immigration from north African countries[17]. Since their introduction, the subtype B clade has predominated in most Western and Central European countries, while the subtype A clade has been predominant in Eastern Europe[19]. HIV-1 subtype B has been responsible for what is often called the "Western epidemic" in Europe and has remained the dominant clade despite the introduction of non-B clades from later migrating populations[19].

Migration from West Africa to Europe seems to be a potential source of HIV-1 non-B variant mobility, with a suspected route through the Maghreb and eventually reaching southern Europe, a region where the HIV-1 non-B variants have significantly increased in the past 10–15 years[17]. Drug resistance profiles are impacted by HIV genetic differences between different subtypes, reinstating the importance of continuous surveillance programs for the early detection of new variants spreading before they become more prevalent and permanently established[17]. Lastly, the need to identify circulating resistance profiles is essential not only for migrants but on the various infected populations to ensure a structured surveillance program.

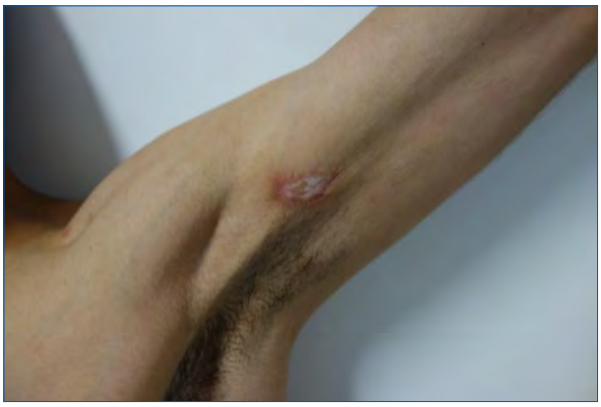

Figure 1. Clinical pictures of lues maligna.

Effective awareness-raising and prevention interventions for migrant populations most affected by HIV are essential to address this epidemic, as well as diminishing barriers to the provision and update of services for migrants.

Lymphogranuloma venereum (LGV)

Lymphogranuloma venereum (LGV) is an STI caused by L1, L2, and L3 serovars of *Chlamydia trachomatis* (CT) that classically manifest as an ulcer in the site of inoculation and lymphadenopathy; it can be transmitted through unprotected vaginal, anal, or oral sexual contact. LGV as a disease was described in 1833 to become a clinical entity only in 1913 by Durand, Nicolas, and Favre[20]. LGV is endemic in tropical and subtropical areas of the world (certain areas of Africa, Southeast Asia, India, the Caribe, and South America), with a reduced incidence in most developed countries[20]. Nonetheless, outbreaks have been reported in North America, Europe, and Australia, mainly as proctitis among MSM; and it is believed that LGV is substantially underdiagnosed in MSM across Europe[21]. One of the first published reports on LGV in Europe dates from 1989, when 27 cases of LGV were identified in Paris, the first in 1981 (Table 1)[22]. Of the 27 cases, 14 were natives from LGV-endemic countries. Since 2003 LGV has been reported endemic among MSM in some European countries[23].

Early recognition and diagnosis are essential to ensure adequate and prompt treatment, which is currently longer in duration when compared to non-LGV CT, and to prevent LGV complications such as fissures, perirectal abscess, as well as systemic symptoms such as fever, fatigue, and weight loss[21,23,24]. Delayed LGV diagnosis is common in European countries due to several factors: availability of diagnostic tests is scarce, LGV is commonly misdiagnosed, and asymptomatic infection is not rare[21]. For instance, a recent report from three European countries that tested 500 specimens from CT-positive MSM rectal swabs found an LGV positivity of 25.6%[21].

The lack of proper LGV diagnosis and surveillance hampers infection control measures, and it seems likely that LGV is continuing to be spread unchecked in MSM in many countries across Europe and beyond. Unified infection control efforts are needed to overcome barriers to implementing LGV testing, establish effective surveillance programs, and optimize diagnosis, treatment, and prevention of LGV.

Zika virus disease (ZIKV)

Zika virus (ZIKV) is an arthropod-borne virus from the Flaviviridae family. ZIKV was first isolated from a nonhuman primate in 1947, from mosquitoes in 1948 in Africa, and the first ZIKV infection in humans dated from 1954 in Nigeria[25]. Since then, ZIKV has spread across the globe, with the first reported outbreak of Zika fever in 2007 in the Federated States of Micronesia[26]. This was followed by other outbreaks in the Pacifica area, leading to 2015, when ZIKV caused an epidemic of unprecedented magnitude in the Americas, which resulted in recognition of the teratogenic effects of ZIKV on the developing fetal brain first reported in 2015 in Brazil[27].

Most of the arboviruses, such as ZIKV, cause zoonoses that usually depend on nonhuman animal species for maintenance in nature, as humans are accidental hosts and an arthropod that acts as vector [mainly *Aedes aegypti*, and secondarily, *Aedes albopictus (A. albopictus)*][28]. The most common mode of biological transmission is infection during a viremic blood meal and injection of infectious saliva during blood feeding (horizontal transmission)[25]. The capacity of arboviruses to adapt to new vectors may have a major impact on the geographic expansion of arboviruses[28]. Other non-vector-borne transmission modes include sexual transmission and maternal-fetal transmission[25].

The first imported case of Zika fever in Europe was reported by a German traveler infected in Thailand in November 2013 (Table 1)[29]. In March 2016, surveillance of ZIKV disease started in EU/EEA[27]. The main objectives were early detection of locally-acquired cases in the EU/EEA and timely reporting of travel-associated cases, particularly those residing in areas of the EU/EEA where *A. albopictus* is established in order to trigger appropriate control measures[27].

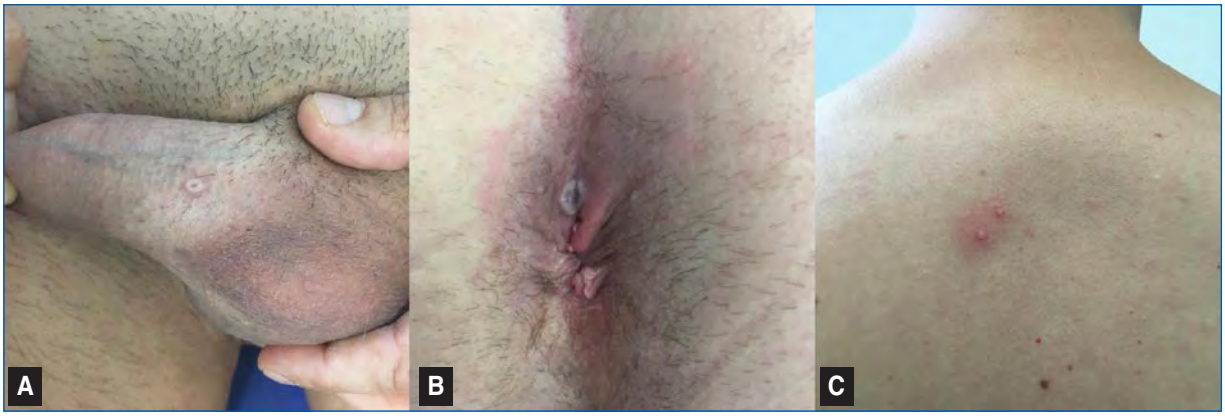

Figure 2. Clinical pictures of MPX infection. **A:** white umbilicated papule. **B:** whitish papule with a necrotic center in an erythematous background. **C:** two whitish papules in an erythematous background on the trunk.

In 2019, France reported three autochthonous, vector-borne cases of ZIKV disease, thus establishing that *A. albopictus* in Europe is a competent vector of ZIKV[30]. Nonetheless, taking into consideration the changes in local populations and the limited window for transmission during the warmer months in the northern hemisphere, the real capability for sustained transmission remains limited[27]. However, climate changes will allow further expansion of the vector in Europe, especially in densely populated cities, through the heat island effect, a phenomenon that must be accounted for by ZIKV spread[31].

The impact of ZIKV in Europe has been limited to returning travelers, a few sporadic locally-acquired cases due to sexual transmission, and for the first time in 2019, three autochthonous vector-borne transmissions[27]. Despite the evidence of limited competence of European *A. albopictus* populations in transmitting ZIKV, continued surveillance, with a particular focus on returning travelers, is mandatory to ensure early detection of risk areas and outbreaks, as well as an efficient public health response.

Mpox

In 1970, the Mpox virus (MPX-V), a zoonotic orthopox DNA virus related to the virus that causes smallpox, was first in the Democratic Republic of Congo[32]. MPX endemic transmission has been reported in some African countries, with few outbreaks and travel-associated cases outside Africa, always with limited secondary spread and human-to-human transmission[33,34].

Since early May 2022, more than 52,000 MPX infections and 18 deaths have been reported in more than 102 countries, prompting the WHO to declare MPX an "evolving threat of moderate public health concern" on 23rd June 2022[35,36]. The classic described mode of transmission of MPX-V is direct lesion-to-skin contact; nonetheless, there has been very little evidence of household spread of any form of MPX besides caregivers, which may indicate that this infection is not easily spread through casual contact and probably requires prolonged or repeated exposure, such as during sexual contact[37]. The recent 2022 outbreak is characterized by a papular skin eruption, fever, and lymphadenopathies (Figure 2), and most cases are mild and self-limited with no need for hospitalization or antiviral treatment; however, described MPX complications include pneumonitis, encephalitis, keratitis, secondary bacterial infections, deep tissue MPX abscess, myocarditis, and epiglottitis[38–40].

In Europe, MPX was first detected in the United Kingdom as an isolated case imported from Nigeria, an endemic country for MPX-V, followed by a hasty detection across other European Countries with an increasing number of cases (Table 1)[41]. Phylogenetic analyses suggest that the virus has circulated undetected for some time outside areas where it has been endemic, possibly masquerading as other STIs.[42] The MPX 2022 outbreak also suggests changes in the biological characteristics of the virus, changes in human behavior, or both. These transformations are suspected to be driven by declining smallpox immunity, relaxation of coronavirus disease 2019 prevention measures, resumption of international travel, and sexual interactions associated with large gatherings[40].

The current MPX outbreak provides a new set of challenges to patients as well as to the healthcare and research communities. Previous lessons learned during the HIV and Covid-19 emergence should support the delivery of a more efficient and effective response to mpox. In turn, the response to MPX should strengthen the reaction to the inevitable next emerging or reemerging infectious disease of pandemic potential.

Conclusion

Over the last century, the world has experienced the impact that population movements can have on infectious diseases. As we move to an era where travel and migration are more accessible than ever before, we are expected to face new challenges when it comes to infectious diseases - and STIs are no different. The last few years have proved that the health authorities and providers must move on from the STI stigma and ensure timely infection management.

Improving access to healthcare for migrants arriving from highly endemic countries helps to identify, through screening, the groups most at risk for increased STIs prevalence while also being cost-effective in nature. Vaccination programs also provide a prevention strategy able to reduce disease burden. Integrating migrants into the local healthcare system ensures that disease cases are adequately managed while accurately defining incidence cases.

Because pathogens know no borders, the world needs to move cohesively and swiftly. Clinical care services must be expanded and strengthened, working in web-based systems to ensure that new pathogens are readily identified and targeted, safeguarding the population's health.

What does the study add?

- Review on imported sexually transmitted infections (STIs) focusing on European epidemiological data.
- Highlights the need for healthcare services to work in web-based systems to safeguard populations.
- Suggestions to mitigate the emergence and spread of STIs.

Funding

None.

Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

References

1. World Health Organization (WHO). Global health sector strategies on, respectively, HIV, viral hepatitis and. sexually transmitted infections for the period 2022-2030. Accessed 13th September, 2022. https://www.who.int/publications/i/item/9789240053779
2. Fuchs W, Brockmeyer NH. Sexually transmitted infections. J Dtsch Dermatol Ges. 2014;12(6):451–64.
3. Vivancos R, Abubakar I, Hunter PR. Foreign travel, casual sex, and sexually transmitted infections: systematic review and meta-analysis. Int J Infect Dis. 2010;14:e842-51.
4. European Centre for Disease Prevention and Control (ECDC). Public Health Guidance on Screening and Vaccination for Infectious Diseases in Newly Arrived Migrants within the EU/EEA Public Health Guidance on Screening and Vaccination for Infectious Diseases in Newly Arrived Migrants within the EU/EEA Ii This Report. doi:10.2900/154411.
5. Hawkes SJ, Hart GJ. Travel, migration and HIV. AIDS Care. 2007;5(2):207–14.
6. Memish ZA, Osoba AO. International travel and sexually transmitted diseases. Travel Med Infect Dis. 2006;4(2):86–93.
7. Khyatti M, Trimbitas RD, Zouheir Y, Benani A, El Messaoudi MD, Hemminki K. Infectious diseases in North Africa and North African immigrants to Europe. Eur J Public Health. 2014;24:47–56.
8. Spiteri G, Unemo M, Mårdh O, Amato-Gauci AJ. The resurgence of syphilis in high-income countries in the 2000s: a focus on Europe. Epidemiol Infect. 2019;147:e143.
9. Tampa M, Sarbu I, Matei C, Benea V, Georgescu SR. Brief history of syphilis. J Med Life. 2014;7(1):4–10.
10. Theo V, Stephen S L, Abbafati C, *et al*. Global burden of 369 diseases and injuries in 204 countries and territories, 1990 -2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet. 2020;396(10258):1204-1222.
11. Singh AE, Romanowski B. Syphilis: review with emphasis on clinical, epidemiologic, and some biologic features. Clin Microbiol Rev. 1999;12:187–209.
12. GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet. 2020;396:1204–22.
13. Harper KN, Zuckerman MK, Harper ML, Kingston JD, Armelagos GJ. The origin and antiquity of syphilis revisited: an appraisal of Old World pre-Columbian evidence for treponemal infection. Am J Phys Anthropol. 2011;146:99–133.
14. Tatu L, Bogousslavsky J. Tabes dorsalis in the 19th century. The golden age of progressive locomotor ataxia. Rev Neurol (Paris). 2021;177(4):376–84.
15. Tucker JD, Shah S, Jarell AD, Tsai KY, Zembowicz A, Kroshinsky D. Lues maligna in early HIV infection case report and review of the literature. Sex Transm Dis. 2009;36(8):512–4.
16. Matic S, Lazarus J V, Donoghoe MC. HIV/AIDS in Europe - Moving from death sentence to chronic disease management. World Heal Organ Reg Off Eur. Published online 2006.
17. Khyatti M, Trimbitas RD, Zouheir Y, Benani A, El Messaoudi MD, Hemminki K. Infectious diseases in North Africa and North African immigrants to Europe. Eur J Public Health. 2014;24:47–56.
18. European Centre for Disease Prevention and Control (ECDC). HIV and Migrants Monitoring Implementation of the Dublin Declaration on Partnership to Fight HIV/AIDS in Europe and Central Asia: 2017 Progress Report HIV and Migrants. 2017.
19. Beloukas A, Psarris A, Giannelou P, Kostaki E, Hatzakis A, Paraskevis D. Molecular epidemiology of HIV-1 infection in Europe: an overview. Infect Genet Evol. 2016;46:180–9.
20. Ceovic R, Gulin SJ. Lymphogranuloma venereum: diagnostic and treatment challenges. Infect Drug Resist. 2015;8:39–47.
21. Cole MJ, Field N, Pitt R, Amato-Gauci AJ, Begovac J, French PD, *et al*. Original research: substantial underdiagnosis of lymphogranuloma venereum in men who have sex with men in Europe: preliminary findings from a multicentre surveillance pilot. Sex Transm Infect. 2020;96(2):137.

22. Scieux C, Barnes R, Bianchi A, Casin I, Morel P, Perol Y. Lymphogranuloma venereum: 27 cases in Paris. J Infect Dis. 1989;160(4):662–8.
23. de Vries HJC, de Barbeyrac B, de Vrieze NHN, Viset JD, White JA, Vall-Mayans M, *et al*. 2019 European guideline on the management of lymphogranuloma venereum. J Eur Acad Dermatol Venereol 2019;33(10):1821–8.
24. Lanjouw E, Ouburg S, de Vries H, Stary A, Radcliffe K, Unemo M. 2015 European guideline on the management of Chlamydia trachomatis infections. Int J STD AIDS. 2016;27(5):333–48.
25. Musso D, Gubler DJ. Zika Virus. Clin Microbiol Rev. 2016;29(3):487–524.
26. Duffy MR, Chen T-H, Hancock WT, Powers AM, Kool JL, Lanciotti RS, *et al*. Zika virus outbreak on Yap Island, Federated States of Micronesia. N Engl J Med. 2009;360(24):2536–43.
27. European Centre for Disease Prevention and Control (ECDC). Zika. virus disease-Annual Epidemiological Report for 2019. ECDC. Published online 2021.
28. Gubler DJ. The global emergence/resurgence of arboviral diseases as public health problems. Arch Med Res. 2002;33(4):330–42.
29. Tappe D, Rissland J, Gabriel M, Emmerich P, Gunther S, Held G, *et al*. First case of laboratory-confirmed Zika virus infection imported into Europe, November 2013. Euro Surveill. 2014;19(4):20685.
30. Giron S, Franke F, Decoppet A, Cadiou B, Travaglini T, Thirion L, *et al*. Vector-borne transmission of Zika virus in Europe, southern France, August 2019. Euro Surveil. 2019;24(45):1900655.
31. Oliveira S, Rocha J, Sousa CA, Capinha C. Wide and increasing suitability for Aedes albopictus in Europe is congruent across distribution models. Sci Rep. 2021;11 (1):9916.
32. Ladnyj ID, Ziegler P, Kima E. A human infection caused by monkeypox virus in Basankusu Territory, Democratic Republic of the Congo. Bull World Health Organ. 1972;46(5):593–7.
33. Hutin YJF, Williams RJ, Malfait P, Pebody R, Loparev VN, Ropp SL, *et al*. Outbreak of human monkeypox, Democratic Republic of Congo, 1996 to 1997. Emerg Infect Dis. 2001;7(3):434–8.
34. Bunge EM, Hoet B, Chen L, Lienert F, Weidenthaler H, Baer LR, *et al*. The changing epidemiology of human monkeypox—a potential threat? A systematic review. PLoS Negl Trop Dis. 2022;16(2):e0010141.
35. World Health Organization (WHO). Multi-country outbreak of monkeypox, External situation report #5 - 7 September 2022. Accessed 16th September, 2022. https://www.who.int/publications/m/item/multi-country-outbreak-of-monkeypox--external-situation-report--5---7-september-2022
36. World Health Organization (WHO). Second meeting of the International Health Regulations. (2005) (IHR) Emergency Committee regarding the multi-country outbreak of monkeypox. Published 2022. Accessed 24th July, 2022. https://www.who.int/news/item/23-07-2022-second-meeting-of-the-international-health-regulations-(2005)-(ihr)-emergency-committee-regarding-the-multi-country-outbreak-of-monkeypox
37. Lane HC, Fauci AS. Monkeypox — past as prologue. N Engl J Med. 2022;387:749–50.
38. Adler H, Gould S, Hine P, Snell LB, Wong W, Houlihan CF, *et al*. Clinical features and management of human monkeypox: a retrospective observational study in the UK. Lancet Infect Dis. 2022;0:1153–62.
39. Huhn GD, Bauer AM, Yorita K, Graham MB, Sejvar J, Likos A, *et al*. Clinical characteristics of human monkeypox, and risk factors for severe disease. Clin Infect Dis. 2005;41:1742–51.
40. Thornhill JP, Barkati S, Walmsley S, Rockstroh J, Antinori A, Harrison LB, *et al*. Monkeypox virus infection in humans across 16 Countries - April-June 2022. N Engl J Med. 2022;387:679–91.
41. Vivancos R, Anderson C, Blomquist P, Balasegaram S, Bell A, Bishop L, *et al*. Community transmission of monkeypox in the United Kingdom, April to May 2022. Euro Surveil. 2022;27:2200422.
42. Áine O, Andrew R. Initial observations about putative APOBEC3 deaminase editing driving short-term evolution of MPXV since 2017 - Monkeypox / Evolution - Virological. Accessed 16th September, 2022. https://virological.org/t/initial-observations-about-putative-apobec3-deaminase-editing-driving-short-term-evolution-of-mpxv-since-2017/830

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CASE REPORT

Behçet's disease as a differential diagnosis of acute genital ulcer: a case report

Doença de Behçet como diagnóstico diferencial de úlcera genital aguda: relato de caso

Giulia Marchetti[a], Iramaia Cardoso-Vasquez[b], and Adriana Bittencourt-Campaner[c]*

Department of Obstetrics and Gynecology, Irmandade de Misericórdia da Santa Casa de São Paulo, São Paulo, Brazil
[a]ORCID: 0000-0001-6633-3340; [b]ORCID: 0000-0003-0018-7082; [c]ORCID: 0000-0002-3044-3019

Abstract

Acute genital ulcers (AGU) have numerous etiologies and are a frequent complaint in the emergency room. Its diagnosis is mostly clinical and initially approached in a syndromic manner. It is based on history, physical examination, and laboratory findings. It is known that genital ulcer can be the first manifestation of Behçet's disease (BD) and its early recognition can prevent clinical complications related to the disease and improve the patient's quality of life. The present article aims to report the case of a patient with an extensive and deep ulcerative lesion of the vulva, who was initially treated with acyclovir due to the suspicion of genital herpes. Subsequently, after the condition worsened and when adequate anamnesis was collected, diagnostic criteria for BD were identified and the correct treatment was started, with therapeutic success. From the above, it is essential that the gynecologist focuses on BD as one of the differential diagnoses for acute genital ulcer.

Keywords: Behçet syndrome. Diagnosis. Differential. Female genitalia. Ulcer.

Resumo

As úlceras genitais agudas possuem inúmeras etiologias e são uma queixa frequente de procura ao pronto socorro. Seu diagnóstico é majoritariamente clínico e inicialmente abordado de forma sindrômica. É baseado na história, exame físico e achados laboratoriais. Sabe-se que a úlcera genital pode ser a primeira manifestação da doença de Behçet e seu reconhecimento precoce pode evitar complicações clínicas relacionadas à doença, além de melhorar a qualidade de vida da paciente. O presente artigo teve como objetivo relatar caso de paciente com lesão ulcerosa extensa e profunda da vulva, que foi inicialmente tratada com aciclovir, pela suspeita de herpes genital. Posteriormente, após piora do quadro e ao coletar-se anamnese adequada, identificou-se critérios diagnósticos para doença de Behçet e iniciou-se o tratamento correto, com sucesso terapêutico. Do exposto, é fundamental que o ginecologista se atente à doença de Behçet como um dos diagnósticos diferenciais para úlcera genital aguda.

Palavras-chave: Diagnóstico. Diferencial. Genitália feminina. Síndrome de Behçet. Úlcera.

***Corresponding author:**
Giulia Marchetti
E-mail: dra.giuliamarchetti@gmail.com

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Introduction

Acute genital ulcers (AGU) are a frequent cause of emergency room visits and can be located in the anogenital area or vagina. Its diagnosis is mostly clinical and initially approached from a syndromic point of view. It is based on history, physical examination, and, in some cases, laboratory findings. AGU can be categorized into infectious and noninfectious groups[1]. Sexually transmitted infections are the main representative of the first group and include herpes simplex, syphilis, lymphogranuloma venereum, chancroid, and donovanosis. Among the most prevalent nonsexually transmitted infectious agents, the Epstein-Barr virus and *Cytomegalovirus* stand out[1–7]. In the group of noninfectious ulcers, the main etiologies are Behçet's disease (BD), Chron's disease, and Lipschütz's ulcer[1].

However, the etiological diagnosis of AGU is difficult since there is a wide variety of causative agents and in many cases, they are poorly recognized by the attending physicians[3]. BD is a multisystem inflammatory disease with vascular involvement, characterized by periods of outbreaks and remission, commonly addressed by rheumatologists[8,9]. However, AGU is one of its first manifestations and the dermatological evaluation is, most of the time, responsible for initially suspecting the diagnosis[9]. The disease can, on many occasions, develop into a serious clinical condition, compromising the patient's health if the diagnosis is not made immediately.

The doctor in the emergency room is frequently faced with AGU and must be prepared to adequately identify its various etiologies. It is essential that they recognize the characteristics of Behçet's ulcer in order to avoid misdiagnosis and delay in the treatment of the disease. Thus, the objective of the present study is to report a case of a patient with extensive and deep ulcers triggered by BD, as well as to discuss the clinical and pathological findings and to carry out a brief review of the literature on the syndromic approach to AGU.

Case description

The present work was approved by the Research Ethics Committee of Irmandade de Misericórdia da Santa Casa de São Paulo Hospital and the patient signed a free and informed consent form for publication. A 31-year-old female patient sought the emergency department complaining of multiple painful vulvar ulcers that had started 1 day before. She was initially treated with oral acyclovir due to suspected genital herpes. After 3 days of treatment, she observed an important and progressive worsening of the condition and returned to the emergency room. On return, she presented herself with several ulcerative lesions on the vulva, with well-defined, deep, and very painful edges located in the labia majora, and introitus. The ulcers had a necrotic background, some with a violet halo around them (Figures 1 and 2). No changes were seen in the vagina and cervix.

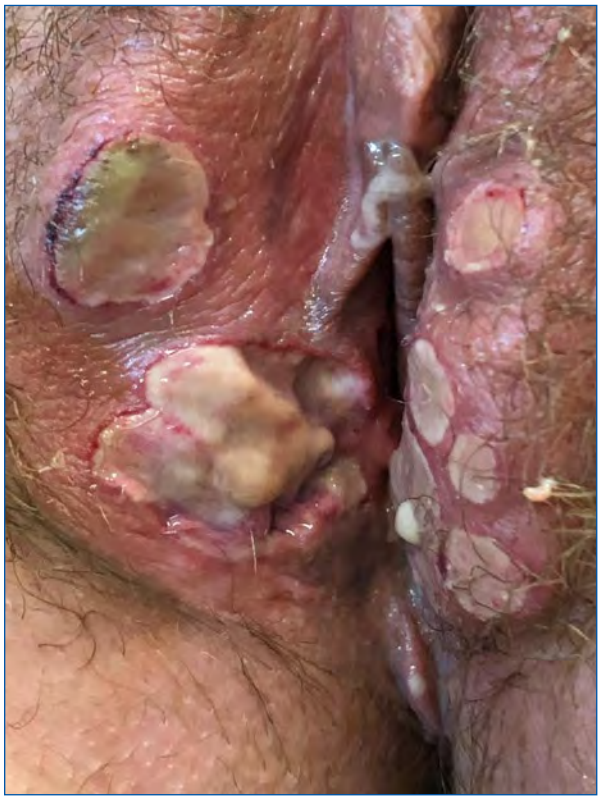

Figure 1. Deep, extensive, confluent, and well-defined acute vulvar genital ulcers with well-defined edges characterize Behcet's disease-related genital ulcers.

The patient denied previous illnesses or surgeries, use of medication, or risky sexual behavior. She had a previous natural delivery and active sexual life with a steady partner, using oral hormonal contraception. The patient's mother was diagnosed with systemic lupus erythematosus.

She was hospitalized and treated with intravenous corticosteroids due to suspicion of BD or Lipschütz ulcer, debridement of ulcers, and local hygiene were also performed. Serologies were performed for herpes simplex, human immunodeficiency virus, *Cytomegalovirus*, syphilis, and all results were negative. Complementary tests such as blood count, erythrocyte sedimentation, and antinuclear factor did not show relevant changes.

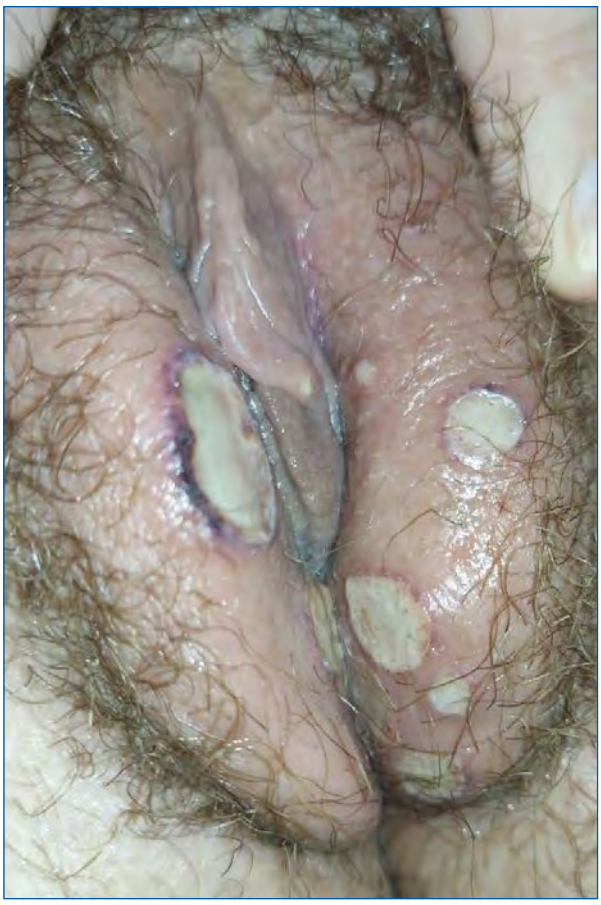

Figure 2. Deep, extensive, confluent, and well-defined acute vulvar genital ulcers with well-defined edges characterize Behcet's disease-related genital ulcers.

There was an improvement of the lesions, and she was discharged after 7 days; home use of prednisone 20 mg/day and referral to a rheumatologist were advised. Complete improvement of the vulvar lesions occurred in about 40 days. In the subsequent detailed anamnesis, she reported a history of recurrent oral ulcers since adolescence, with about seven episodes per year, in addition to nonspecific and intermittent polyarthralgia without a definitive diagnosis. Thus, her previous history and the presented evolution of the case confirmed the diagnosis as BD. Treatment with prednisone 20 mg daily was maintained and oral colchicine was introduced. The patient is doing well, with no further lesions.

Discussion

Among the noninfectious etiologies of AGU that can affect women, BD is important due to the high prevalence, as well as the severity of the disease. The most common clinical manifestations of BD are recurrent oral and genital ulcers, skin lesions (erythema nodosum, pustular lesions, pyoderma gangrenosum, and superficial thrombophlebitis), uveitis, in addition to multiple other less common systemic manifestations. It is not a disease with chronic and persistent inflammatory activity; recurrent attacks of acute inflammation are more common. Although most of its manifestations are considered benign and self-limiting, the involvement of the central nervous system and large vessels, a less usual manifestation, can be severe or progressive, with significant lethality[8,10].

The AGU associated with BD is generally characterized by defined borders, with an erythematous or violet halo, associated with a yellowish or greyish pseudomembrane, and a necrotic background. Lesions tend to form scars and genital sequelae[8]. The pain component is also present but may be a confounding factor with other etiologies.

Behçet's disease (BD) has its complete pathophysiology unknown. It is known that some viral and bacterial infectious agents can behave as instigators of the inflammatory response behind the disease. However, several theories are still being investigated and none completely justifies the development of the disease, which makes it difficult to standardize an effective diagnostic test. The genetic correlation with the HLA-B51 class I antigen is important in pathogenesis, but its presence alone is not sufficient to explain all of the observed symptoms[8]. Therefore, it is difficult to predict risk factors for the development of the condition, while an adequate anamnesis and physical examination are essential since the diagnosis is fundamentally clinical.

There are numerous diagnostic classifications proposed for the disease based on the patient's symptoms, but there are no definitive satisfactory complementary tests to confirm the diagnosis[11]. The international criteria of the BD should always include the major criteria of recurrent oral ulcers (at least three times in 1 year) and at least two minor criteria, such as recurrent genital ulcers, eye lesions, skin lesions, or positive pathergy test, in the absence of any clinical explanation[12]. Other classifications described in the literature are widely used and present variations of the International criteria, such as those by C.G. Barnes and H. Yazici and the International Team for the Revision of the International Criteria for BD (2014)[13,14].

In the case reported, the patient's ulcer contemplated the characteristics of a lesion commonly described in BD. However, an erroneous initial etiological diagnosis of AGU was made since the pain component was valued and not associated with other characteristics of the

lesion. Herpes simplex was first treated with acyclovir. The syndromic approach to AGU recommended by the Ministry of Health of our country initially includes the treatment of herpes simplex as it is one of the most common etiologic agents in cases of AGU[1,2,15].

A complete anamnesis was performed later and personal and family history, such as oral ulcers in adolescence, intermittent polyarthralgia, and maternal autoimmune disease, were only considered after years of symptoms. This could have elucidated the condition and contributed to the delay in diagnosis and treatment.

The morbidity and mortality of BD are significant and early treatment can improve the quality of life, avoiding irreversible damage and exacerbation of the disease since there is no cure. The treatment regimen is varied and involves the use of immunomodulatory and anti-inflammatory drugs to induce and maintain the remission of the condition[9]. In the case under study, the proper use of medications promoted complete improvement of symptoms without recurrence of lesions.

Conclusion

AGU can be the first clinical manifestation of BD, and the dermatological evaluation can be responsible for initially suspecting the diagnosis when faced with this complaint in the emergency room. It is essential that everyone should be able to recognize the characteristics of Behçet's ulcer and invest a few minutes of care in improving the anamnesis to avoid delay in the diagnosis. In that way, the patient's quality of life will be assured. Thus, understanding the syndromic approach to AGU is extremely important in the medical field.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Conflicts of interest

None.

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References

1. Workowski KA. Centers for disease control and prevention sexually transmitted diseases treatment guidelines. Clin Infect Dis. 2015;61: S759–62.
2. Farhi D, Wendling J, Molinari E, Raynal J, Carcelain G, Morand P, *et al*. Non-sexually related acute genital ulcers in 13 pubertal girls: a clinical and microbiological study. Arch Dermatol. 2009;145:38–45.
3. Cheng SX, Chapman MS, Margesson LJ, Birenbaum D. Genital ulcers caused by Epstein-Barr virus. J Am Acad Dermatol. 2004;51:824–6.
4. Kuloğlu Z, Kansu A, Demirçeken F, Bozkir M, Kundakçi N, Bingöl-Koloğlu M, *et al*. Crohn's disease of the vulva in a 10-year-old girl. Turk J Pediatr. 2008;50:197–9.
5. Halvorsen JA, Brevig T, Aas T, Skar AG, Slevolden EM, Moi H. Genital ulcers as initial manifestation of Epstein-Barr virus infection: two new cases and a review of the literature. Acta Derm Venereol. 2006;86:439–42.
6. Barnes CJ, Alió AB, Cunningham BB, Friedlander SF. Epstein-Barr virus-associated genital ulcers: an under-recognized disorder. Pediatr Dermatol. 2007;24:130–4.
7. Cebesoy FB, Balat O, Inaloz S. Premenarchal vulvar ulceration: is chronic irritation a causative factor? Pediatr Dermatol. 2009;26:514–8.
8. Scherrer MAR, Rocha VB, Garcia LC. Behçet's disease: review with emphasis on dermatological aspects. An Bras Dermatol. 2017;92:452–64.
9. Alpsoy E, Bozca BC, Bilgic A. Behçet Ddisease: an update for dermatologist. Am J Clin Dermatol. 2021;22:477–502.
10. Alpsoy E. Behçet's disease: a comprehensive review with a focus on epidemiology, etiology and clinical features, and management of mucocutaneous lesions. J Dermatol. 2016;43:620–32.
11. Hatemi G, Seyahi E, Fresko I, Talarico R, Hamuryudan V. Behçet's syndrome: a critical digest of the 2014-2015 literature. Clin Exp Rheumatol. 2015;33:S3–12.
12. Criteria for diagnosis of Behçet's disease. International Study Group for Behçet's Disease. Lancet. 1990;335:1078–80.
13. Barnes CG, Yazici H. Behçet's syndrome. Rheumatology (Oxford). 1999;38:1171–4.
14. International Team for the Revision of the International Criteria for Behçet's Disease (ITR-ICBD). The International Criteria for Behçet's Disease (ICBD): a collaborative study of 27 countries on the sensitivity and specificity of the new criteria. J Eur Acad Dermatol Venereol. 2014;28:338–47.
15. Araujo MAL, Uesono J, Machado NMDS, Pinto VM, Amaral E. Brazilian protocol for sexually transmitted infections 2020: approaching sexually active individuals. Rev Soc Bras Med Trop. 2021;54:e2020628.

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CASE REPORT

Scalp angiosarcoma in elderly patient: case report

Angiossarcoma de couro cabeludo em paciente idoso: um relato de caso

*Oona S. Erdmann[1,a], Isabelle L. Lemos[1,b], Karina B. Medeiros[2,c], Juliana E. Jung[3,d], and Eduardo M. de-Castro[1,e]**

[1]Deparment of Medicine, Faculdades Pequeno Príncipe; [2]Deparment of Medicine, Hospital Universitário Evangélico Mackenzie; [3]Deparment of Dermatopathology, Citolab. Curitiba, Paraná, Brazil

[a]ORCID: 0000-0001-8100-7658; [b]ORCID: 0000-0002-9741-1652; [c]ORCID: 0000-0001-8202-6711; [d]ORCID: 0000-0002-1446-7504; [e]ORCID: 0000-0001-6136-2660

Abstract

Cutaneous angiosarcomas are rare, aggressive tumors, and represent < 1% of all malignant head and neck neoplasms. Their highest incidence is in elderly men and Caucasians. The importance of reporting cases of this type of tumor is to emphasize it as a differential diagnosis in the elderly. We report a 90-year-old Caucasian male patient with an erythematous and infiltrative scalp tumor. Surgical resection and anatomopathological evaluation, including immunohistochemical studies, diagnosed a high-grade angiosarcoma. Primary cutaneous angiosarcoma is the main form of angiosarcoma, with rapid evolution, affecting mainly the scalp and face. It presents with varied morphologies, irregular growth, and spontaneous bleeding. Microscopic findings include infiltrating and anastomosing vascular channels lined by atypical endothelial cells, as well as solid growth in high-grade tumors. The prognosis is poor, usually related to the patient's age, lesion site, and disease stage. The variable microscopy may mimic other neoplasms, and a wide spectrum of diseases should be considered in the differential diagnosis.

Keywords: Angiosarcoma. Case report. Immunohistochemistry. Skin.

Resumo

Angiossarcomas cutâneos são tumores raros e agressivos, e representam menos de 1% de todas as neoplasias malignas de cabeça e pescoço. Sua maior incidência é em homens idosos e caucasianos. A importância de relatar casos desse tipo de tumor está em enfatizá-lo com um diagnóstico diferencial em idosos. Relata-se paciente masculino, 90 anos, caucasiano, com tumorações eritematosas e infiltrativas do couro cabeludo. Após ressecção cirúrgica e avaliação anatomopatológica, incluindo estudo imunoistoquímico, diagnosticou-se angiossarcoma de alto grau. O angiossarcoma cutâneo primário é a principal forma de angiossarcoma, possui rápida evolução e acomete principalmente couro cabeludo e face. À macroscopia, apresentam morfologia variada, crescimento irregular e sangramento espontâneo. Achados microscópicos incluem canais vasculares anastomosados e infiltrativos, revestidos por células endoteliais atípicas, bem como crescimento sólido em tumores de alto grau. O prognóstico é mau, geralmente relacionado à idade do paciente, local da lesão e estadio da doença. A microscopia variável pode mimetizar outras neoplasias, devendo-se considerar amplo espectro de doenças no diagnóstico diferencial.

Palavras-chave: Angiossarcoma. Relato de caso. Imuno-histoquímica. Pele.

***Corresponding author:**
Eduardo M. de-Castro
E-mail: medmoca@gmail.com

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Introduction

Cutaneous angiosarcomas are rare and quite aggressive tumors that originate from the cells of the blood or lymphatic vascular endothelium. The incidence is higher in elderly men and Caucasians[1]. Risk factors include radiation, chemical exposure to arsenic, and previous history of chronic lymphedema[2].

Epidemiologically, they represent less than 1% of all malignant neoplasms in the head and neck. In addition, angiosarcomas are described in the literature in other anatomical regions, such as the liver, spleen, bones, and heart[1].

Regarding morphology, they can present as a papule, macula, plaque, or nodule of imprecise limits and variable extension, and hemorrhagic or necrotizing surface. The possibility of resection, presence of metastases, degree of differentiation, and lesion extension are very important prognostic factors[3].

We report a case of angiosarcoma of the scalp, emphasizing the importance of considering it as one of the differential diagnoses in elderly patients since early diagnosis allows an extremely favorable outcome.

Therefore, the objective of this case report is to describe the appearance of angiosarcoma on the scalp of a patient who was being followed up after the excision of nasal basal cell carcinoma. It also aims to perform a literature review on angiosarcoma, approaching its pathophysiology, epidemiological aspects, clinical manifestations, both typical and atypical, and treatment.

Clinical case

A 90-year-old Caucasian male patient, with a history of controlled asthma, presented to a medical consult in October 2020 for the investigation of a rapidly growing lesion on the left nasal wing, measuring 2 cm. Biopsy confirmed basal cell carcinoma. The tumor was surgically removed, and the area was reconstructed. At the time, his medications included turmeric, paracetamol, vitamin B complex (B1, B6, B12), vitamin D, amlodipine, and inhaling fluticasone.

In July 2021, he returned for a follow-up and an investigation of new skin lesions on the scalp. There were changes to his pharmacological therapy, with the removal of the vitamin B complex and turmeric, and the addition of apixaban. Physical examination revealed the presence of two erythematous and infiltrative tumors, named “larger” and “smaller” lesions (Figure 1).

Incisional biopsies of the lesions suggested a poorly differentiated neoplasm infiltrating the dermis.

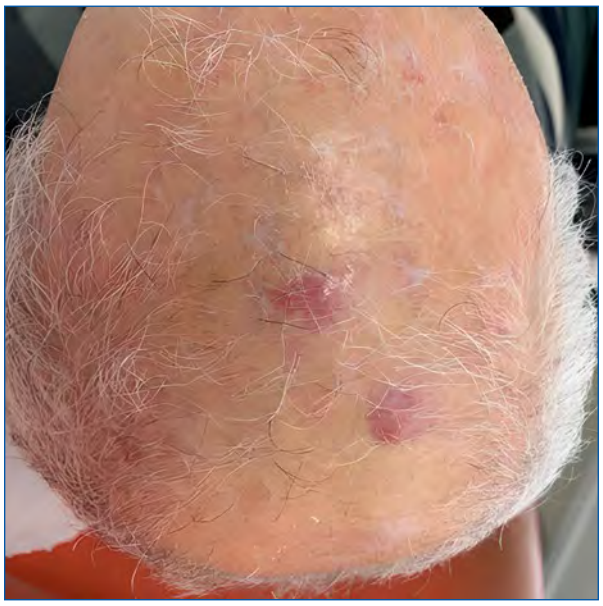
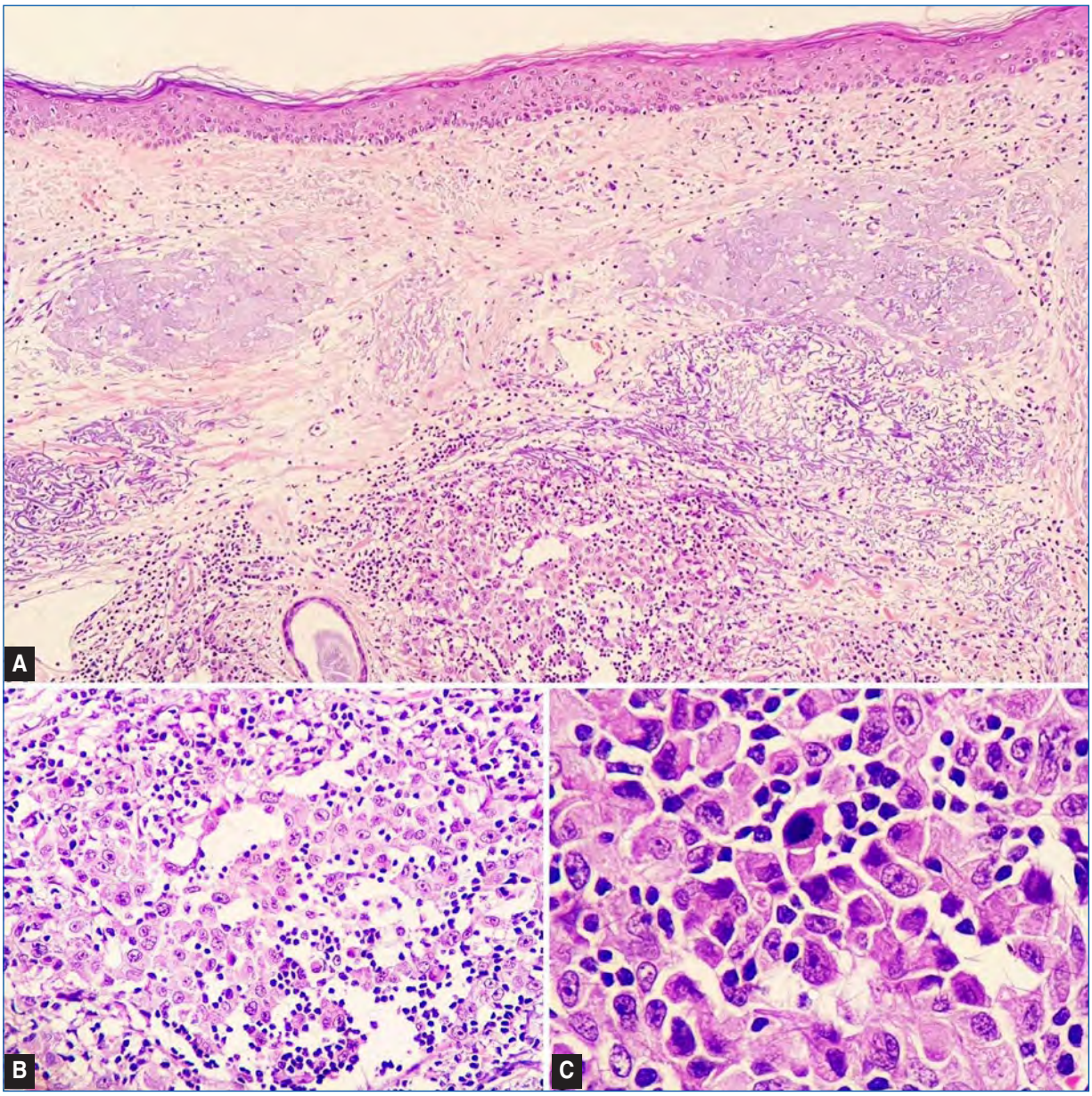


Figure 1. Erythematous lesions on the scalp measuring the largest 3.1 × 2.0 cm and the smallest 2.0 × 1.7 cm.

The patient was then submitted to surgical resection of the lesions, and reconstruction was performed with a left iliac fossa skin graft and rotation flap, and 2nd intention healing area.

Gross anatomopathological evaluation of the surgical specimen showed two contiguous, whitish, elevated, and ill-defined lesions, with 3.1 × 2.0 cm with a maximum thickness of 0.6 cm, and 2.0 × 1.7 cm with a maximum thickness of 0.4 cm. Both were 0.5 cm distant from the radial margin. Microscopic examination revealed a poorly differentiated invasive neoplasm involving the dermis and muscle fascia. The architectural pattern was solid, and there were numerous mitotic figures (Figure 2) and moderate peritumoral lymphocytic infiltrate. Deep and radial surgical margins were clear. The immunohistochemical study, including antibodies for the differential diagnosis between carcinoma, melanoma, and angiosarcoma, confirmed the vascular lineage markers cluster of differentiation 31 (CD31), CD34, D2-40, and friend leukemia integration 1 transcription factor (FLI-1) (Figure 3). Other markers for epithelial and melanocytic lineages were negative. The final diagnosis was high-grade angiosarcoma.

In the immediate postoperative period, the patient presented partial necrosis of the graft. However, approximately one month after the removal of the lesions, the patient was reassessed and the surgical wound was in the process of healing, with no signs of necrosis or infection. The patient underwent ten sessions of adjuvant radiotherapy and was discharged



Figures 2. Histopathological characteristics of the neoplasm. **A:** small magnification, showing the neoplasm occupying dermis (40×, H&E). **B:** atypical cells with permeating lymphocytes (100×, H&E). **C:** detail showing nuclear pleomorphism and mitotic figures (400×, H&E).

(Figure 4). By the end of the treatment, the patient developed metastatic lesions in the trunk and died soon after.

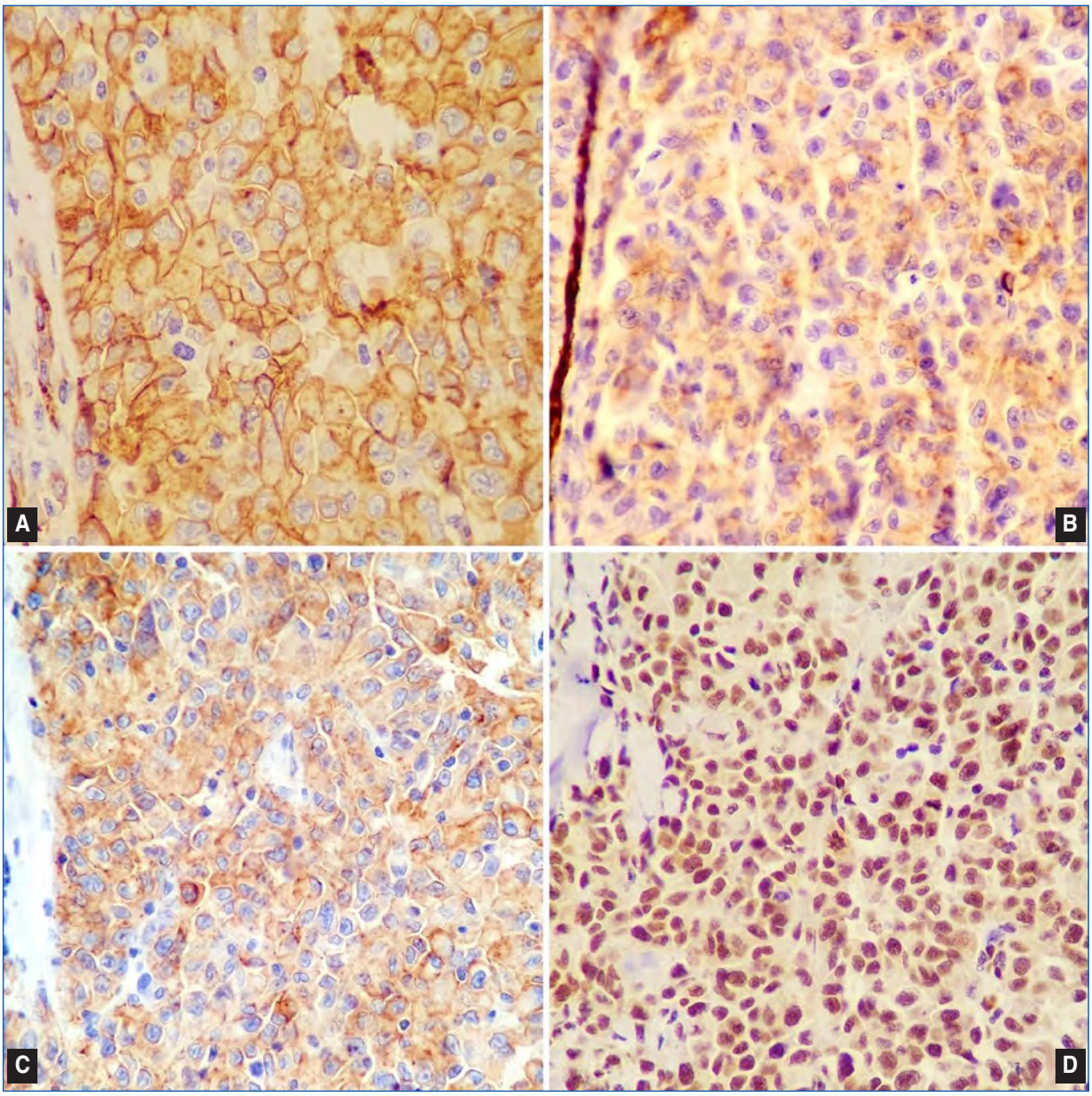
Discussion

Primary cutaneous angiosarcoma is the main form of angiosarcoma, which evolves rapidly, and the main affected sites are the scalp and face, the latter being considered the most aggressive topography[4].

Epidemiologically, in angiosarcomas overall, there is no significant prevalence difference between men and women[4], however, when located on the scalp, the prevalence is higher in elderly Caucasian men, as seen in the reported case[5].

Although still much debated, the main hypothesis for the origin of this neoplasm is the endothelium of smaller blood or lymphatic vessels or their progenitor cells[6]. Rarely do these tumors arise from large vessels[5]. Radiotherapy and chronic lymphedema are known risk factors[6].

Macroscopically, the lesion is poorly delimited, and can present in different morphologies-areas of subcutaneous hematoma, bluish macules, peripheral

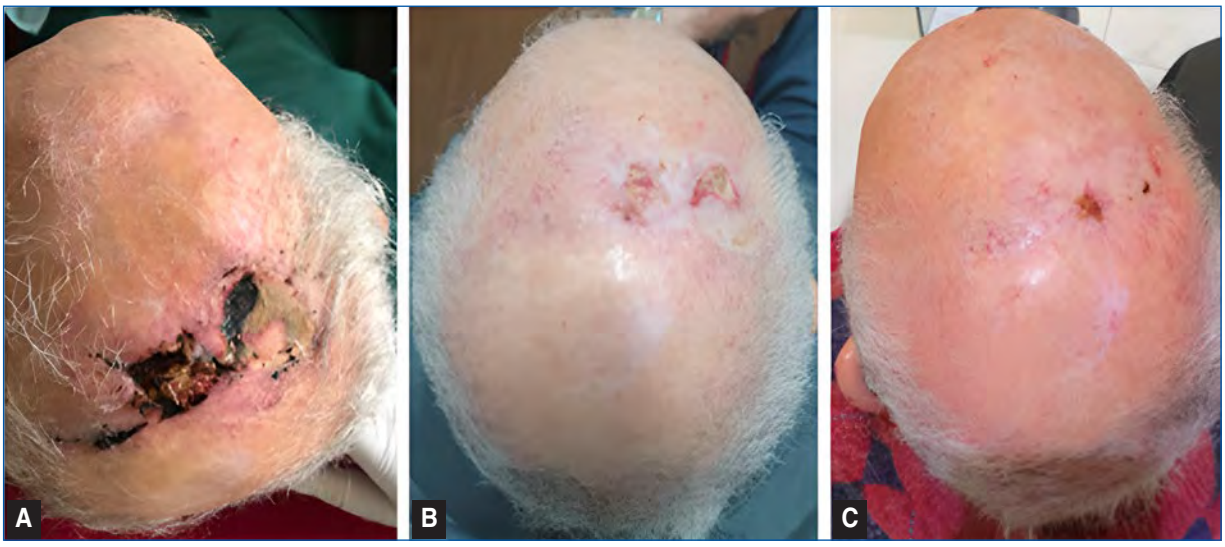


Figures 3. Immunohistochemical characteristics of the neoplasm (100×, IHC). Positivity in neoplastic cells for the markers. **A:** CD34. **B:** CD31. **C:** D2-40. **D:** FLI-1.

erythematous ring and satellite nodules, as reddish, raised papules[7] or as flat, infiltrative plaques[5]. In more advanced stages, lesions can be elevated, nodular, and ulcerated[5]. It has irregular growth and may acquire a multicentric appearance, containing bluish plaques, and nodules within[4]. It tends to bleed spontaneously or due to minimal trauma[4,5].

Microscopically, they are poorly differentiated and can compromise the dermis and soft tissues[5]. From the morphological point of view, they can be classified as low or high-grade lesions. Low-grade angiosarcomas are described as neoplasms of atypical endothelial cells arranged in single or multiple layers, while high-grade angiosarcomas are described as neoplasms of undifferentiated and pleomorphic cells, with disorganized architecture, high mitotic index, and foci of hemorrhage and necrosis[4,5]. The final diagnosis requires immunohistochemistry studies, especially in high-grade neoplasia, with positivity for endothelial markers such as D2-40, CD31, CD34, and FLI-1[8], as in the reported case[4,9].

The prognosis of the neoplasm is poor[3,5,6]. The survival rate is directly associated with patient age, lesion site, and disease stage[7]. Factors favoring a better prognosis



Figures 4. Postoperative evolution. **A:** partial necrosis of the skin graft from the left iliac fossa. **B:** graft healing in the late postoperative period. **C:** after adjuvant radiotherapy.

would be lesions in smaller quantity and size, younger patients, and clear surgical margins[5].

The most effective form of treatment is surgical resection, despite the high recurrence rate and difficulty in achieving free surgical margins[4,5]. Multimodal therapy requires an assessment of the age and the general clinical condition of the patient. Chemotherapy is used in patients with incomplete surgical resection or with distant metastasis, such as lungs, liver, spleen, and cervical lymph nodes[4,6,10].

Radiotherapy is also a viable treatment option, and patients who received it as a form of therapy had a median survival rate four times higher when compared to those who did not use this approach[5].

The combination of surgery and radiotherapy can be associated with a better prognosis when combined with the previously mentioned factors, but only if applied to lesions smaller than 5 cm in diameter[5].

Scalp cutaneous angiosarcoma is the most aggressive form of this neoplasm, affecting mostly elderly Caucasian men. Its main treatment is surgery, which can be complemented with adjuvant chemotherapy or radiotherapy, or both. Despite its rarity, angiosarcoma cannot be ignored as a potential diagnosis since the microscopy is very variable and may mimic other neoplasms such as other sarcomas, melanoma, and carcinomas, which highlights the importance of considering a broad spectrum in the differential diagnosis.

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None.

Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

References

1. Mullins B, Hackman T. Angiosarcoma of the head and neck. Int Arch Otorhinolaryngol. 2015;19:191–95.
2. Vinay K, Abbas A, Aster J. Robbins & Cotran Pathologic Basis of Disease. 10th Edition. Philadelphia. Elsevier. 2020.
3. Grundahl JEH, Hallermann C, Schulze HJ, Klein M, Wermker K. Cutaneous angiosarcoma of head and neck: a new predictive score for loco-regional metastasis. Transl Oncol. 2015;8:169–75.
4. Oley MC, Oley MH, Durry MF, Kepel EM, Farukh M. Cutaneous angiosarcoma: a case report. International Journal of Surgery Case Reports. 2021;88:1–5.
5. Pawlik TM, Paulino AF, Mcginn CJ, Baker LH, Cohen DS, Morris JS, *et al*. Cutaneous angiosarcoma of the scalp: a multidisciplinary approach. Cancer. 2003;98:1716–26.
6. Zhang Y, Yan Y, Zhu M, Chen C, Lu N, Qi F, *et al*. Clinical outcomes in primary scalp angiosarcoma. Oncol Lett. 2019;18:5091–6.
7. Bhatti Z, Bhatti R, Brangman S, Whiting K, Dhamoon A. Extensive cutaneous scalp angiosarcoma. Hindawi. 2018;2018:1–3.
8. Chugh AP, Gandhoke CS, Mohite AG, Khedkar BV. Primary angiosarcoma of the skull: a rare case report. Surg Neurol Int. 2014;92:1–4.
9. Dabbs D. Diagnostic Immunohistochemistry: theranostic and genomic applications. Rio de Janeiro, Brazil. Elsevier. 2018.
10. Vora R, Anjaneyan G, Gupta R. Cutaneous angiosarcoma of head and neck. Indian J Dermatol. 2014;59:632.

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CASE REPORT

Nodular hidradenoma mimicking nodular basal cell carcinoma

Hidradenoma nodular simulando carcinoma basocelular nodular

Elisangela M.A. Lima[1,2,a], Mariana O. Fernandes[1,b], Marina Silva[1,c], Flávia R. Ferreira[1,2,d], and Fernanda G. Moya[3,e]*

[1]Department of Dermatology, Hospital Municipal Universitário de Taubaté (H.MUT/UNITAU); [2]Department of Dermatology, Departamento de Medicina da Universidade de Taubaté, UNITAU; [3]Department of Pathological Anatomy, Hospital do Servidor Público Estadual de São Paulo. São Paulo, Brasil.
[a]*ORCID: 0000-0002-2390-0410*; [b]*ORCID: 0000-0002-3134-7096*; [c]*ORCID: 0000-0001-7474-7033*; [d]*ORCID: 0000-0001-5679-4282*;
[e]*ORCID: 0000-0003-2933-2845*

Abstract

A 40-year-old woman, phototype III, presented with an erythematous, sessile nodule with small ulceration points on the right forearm for 1 year and 6 months. Dermoscopy showed structures similar to blue-gray globules, arboriform telangiectasias with some thickened vessels, bright white spots, and microulceration points. The main hypothesis of nodular basal cell carcinoma (BCC) and excisional biopsy of the lesion were performed. Histopathology showed nodular adnexal epithelial neoplasia without atypia, with a focal connection to the epidermis, a clear cell component, and immunohistochemistry positivity for p63, epithelial membrane antigen (EMA), and cytokeratin AE1/AE3, concluding the diagnosis of nodular hidradenoma. The unusual presentation, mimicking a nodular BCC, and the importance of the correct approach to atypical lesions motivated this report.

***Keywords*:** Acrospiroma. Basal cell Carcinoma. Dermoscopy. Histology. Immunohistochemistry.

Resume

Mulher de 40 anos, fototipo III, apresentando nódulo eritematoso, séssil, com pequenos pontos de ulceração no antebraço direito há um ano e meio. À dermatoscopia visualizadas estruturas semelhantes a glóbulos azul-acinzentados, telangiectasias arboriformes com alguns vasos espessados, manchas branco-brilhantes e pontos de micro ulceração. Realizada hipótese principal de carcinoma basocelular (CBC) nodular e biópsia excisional da lesão. A histopatologia evidenciou neoplasia epitelial anexial nodular sem atipias, com conexão focal com a epiderme e componente de células claras e a imunohistoquímica positividade para p63, antígeno de membrana epitelial (EMA) e citoqueratina AE1/AE3, concluindo o diagnóstico de hidradenoma nodular. A apresentação incomum, simulando um CBC nodular e importância da abordagem correta de lesões atípicas motivaram este relato.

Palavras-chave: Hidradenoma nodular. Carcinoma basocelular. Dermoscopia. Histologia. Imuno-histoquímica.

***Corresponding author:**
Flávia R. Ferreira
E-mail: dermagica@uol.com.br

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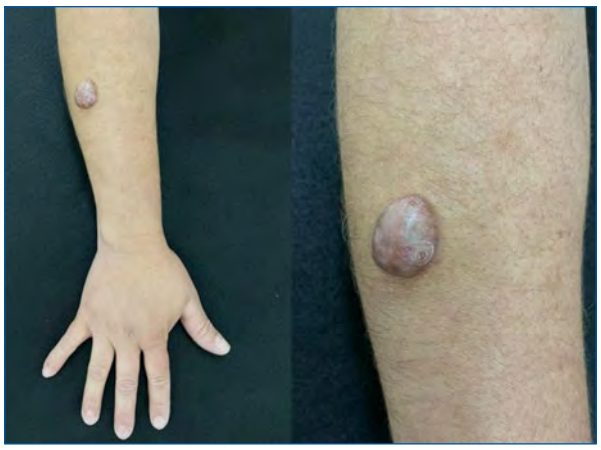

Figure 1. Hyperchromic, erythematous, sessile nodule of firm consistency, and with points of ulceration.

Introduction

Nodular hidradenoma, first described by Mayer in 1941, is a benign adnexal neoplasm with eccrine or apocrine differentiation that occurs in middle-aged adults, mainly women, and with a controversial prevalence in the literature[1-3]. Clinically, it manifests as a solid or cystic nodule, normochromic to erythematous, with a smooth surface, slow and endophytic growing, and with rare cases of exophytic growing. The most common affected locations are the scalp, face, trunk, and proximal extremities[1]. At dermoscopy, the pattern consisting of a homogeneous bluish area that occupies the entire lesion, associated with vascular structures and white dots, is the most common pattern[4]. The unusual presentation, mimicking a nodular basal cell carcinoma (BCC) and the importance of the correct approach to atypical lesions motivated this report.

Clinical case

A 40-year-old female patient, phototype III, complained of a "lump" in her right forearm for a year and a half. Dermatological examination revealed a hyperchromic, erythematous, and sessile nodule (2.5 × 2 cm) of firm consistency and with points of ulceration (Figure 1). History of initial growth and subsequent stabilization, mild pain on manipulation. The diagnostic hypotheses of nodular BCC, dermatofibrosarcoma protuberans, amelanotic melanoma, Merkel cell carcinoma, and adnexal tumors were considered. On dermoscopy, the presence of structures similar to blue-gray globules, arboriform telangiectasias with some thickened vessels, bright white spots, and points of microulceration (Figure 2). An excisional biopsy was performed and the material was sent for histopathological and immunohistochemical examination. Histopathology showed nodular adnexal epithelial neoplasia without atypia, with a focal connection to the epidermis and a clear cell component, and characteristics suggestive of nodular hidradenoma (Figure 3); confirmed by immunohistochemistry with positivity for p63, epithelial membrane antigen (EMA), and cytokeratin AE1/AE3. The patient remains under follow-up with a good surgical scar aspect and no recurrence.

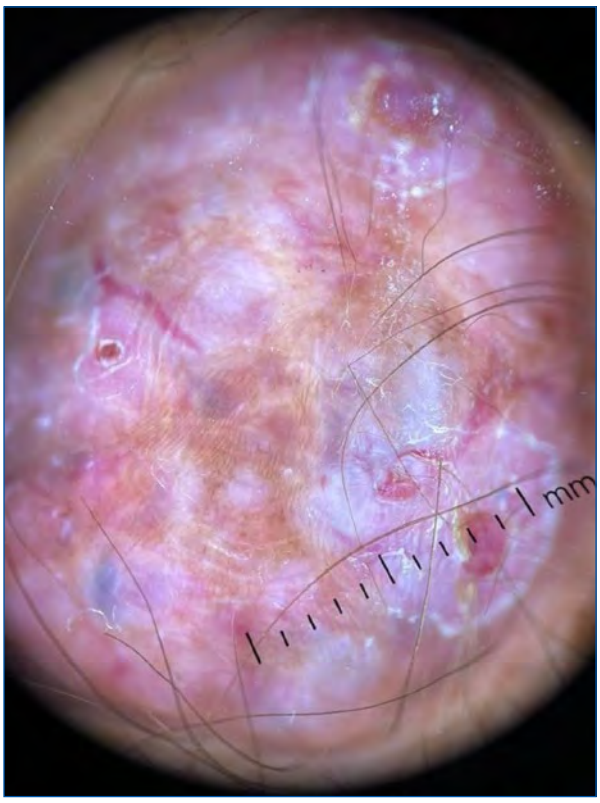

Figure 2. Lesion dermoscopy.

Discussion

Nodular hidradenoma is a benign adnexal neoplasm with eccrine or apocrine differentiation that occurs in middle-aged adults, mainly women[1,2], as observed in this case. The exophytic clinical presentation is rare, however, described in the literature.[1]

There is considerable confusion in the literature regarding the appropriate nodular hidradenoma designation, and it has already been called clear cell hidradenoma, cystic nodule hidradenoma, clear cell myoepithelioma, and eccrine acrospiroma. This reflects different approaches among authors regarding its histological characteristics and histogenesis[1,3].

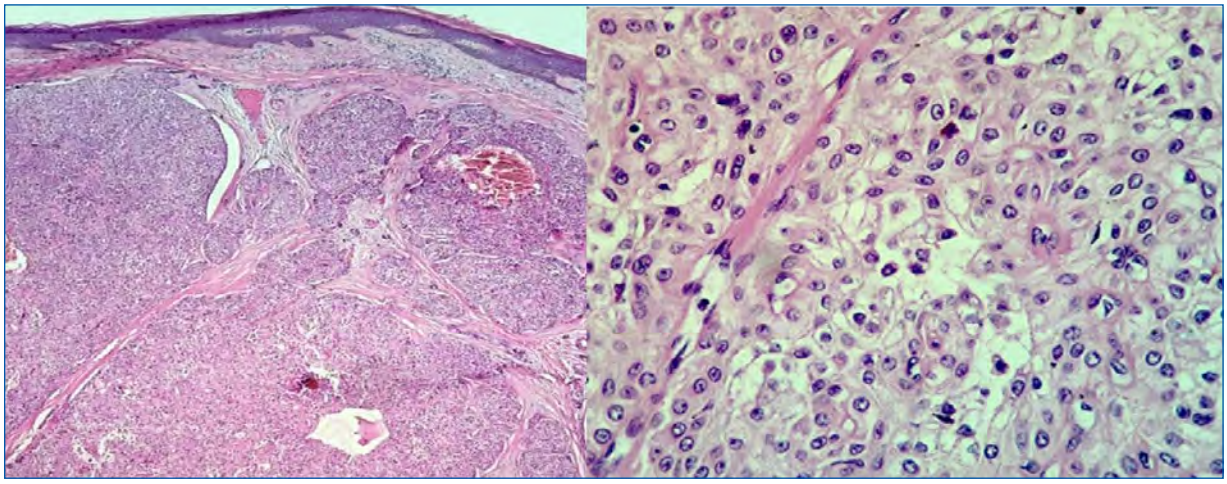

Figure 3. Nodular adnexal epithelial neoplasm without atypia, with a focal connection to the epidermis, and clear cell component (HE 40 and 400X).

The histopathology of nodular hidradenoma is characterized by the presence of a well-circumscribed but not encapsulated tumor. It presents a typical biphasic cell pattern, with polyhedral cells with eosinophilic cytoplasm and large cells with abundant clear cytoplasm and a small nucleus. There is a variable proportion between cell types, but clear cells predominate in one-third of cases[1,2], as seen in this case. Immunohistochemistry shows reactivity for p63, EMA, and cytokeratin AE1/AE2[5], also observed in this case.

Classically, the differential diagnosis includes other adnexal tumors, being clinically indistinguishable[1]. Basal cell carcinoma (BCC) (ulcerated forms) as a differential diagnosis of hidradenoma nodular is rarely cited in the literature[6].

Curative treatment consists of surgical excision, but the possibility of recurrence exists. Malignant transformation is rare[1].

The present report registers an unusual presentation of a nodular hidradenoma, with hyperchromic, ulcerated, and exophytic manifestations, simulating a nodular BCC in the clinical aspect but mainly dermoscopically. We emphasize the importance of the correct approach to atypical lesions by the dermatologist, as well as the fundamental role of complementary exams (histopathology/immunohistochemistry) in the conclusive diagnosis of this case.

Funding

None.

Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

References

1. Sousa VB, Lacerda VC, D'Elia MLN, Alves NTM, Pineiro-Maceira JM, Silva SCMC. Clear cell hidradenoma: atypical presentation on the scalp. Surg Cosmet Dermatol. 2016;8:S735.
2. Nandeesh BN, Rajalakshmi T. A study of histopathologic spectrum of nodular hidradenoma. Am J Dermatopathol. 2012;34:461–70.
3. Kazakov DV, McKee PH, Michal M, Kacerovska D. Lesions with predominant apocrine and eccrine differentiation. In: Dmitry V. Kazakov MD PhD, Cutaneous adnexal tumors. WKL. 2012;p1–171.
4. Serrano P, Lallas A, Del Pozo LJ, Karaarslan I, Medina C, Thomas L, *et al*. Dermoscopy of nodular hidradenoma, a great masquerader: a morphological study of 28 cases. Dermatol. 2016;232:78–82.
5. Canedo T, de Almeida MP, Cuzzi T, Ramos-e-Silva M. Immunophenotypic aspects of cylindroma and nodular hidradenoma. J Eur Acad Dermatol Venereol. 2010:24:178–85.
6. Montealegre Gómez CE, Correa Londoño LA. Hidradenoma de células claras: Presentación de un caso y revisión de la literatura. Rev Asoc Colomb Dermatol Cir Dematol. 1996;5:76–8.

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CASE REPORT

Basal Cell Carcinoma development after use of Metformin - Potential role of Nitrosamines as Enhancing Factors

Desenvolvimento de Carcinoma Baso Celualr após o uso de Metformina – Potencial papel das Nitrosaminas como Fatores Favorecedores

*Georgi Tchernev[1,2,a] and Simona Kordeva[1,b]**

[1]Department of Venereology and Dermatologic Surgery, Onkoderma Clinic for Dermatology; [2]Department of Dermatology and Venereology, Medical Institute of Ministry of Interior. Sofia, Bulgaria

[a]ORCID: 0000-0002-0365-3504; [b]ORCID: 0000-0002-1768-8601

Abstract

The potential or actual contamination of widely distributed medications with nitrosamines is currently a serious problem. Medications, such as ranitidine, metformin, rifampicin, hydrochlorothiazide, angiotensin-converting enzyme (ACE) inhibitors, and sartans, used as monotherapy or in combination with other drug classes, practically contain ingredients potentiating tumor generation and tumor progression. The dilemma with the ˝increased availability˝ of nitrosamines concerns the subsequent development not only of single but also of multiple skin tumors, sometimes even in combination with other tumor types. The development, in particular, of keratinocyte tumors after administering drugs such as sartans, hydrochlorothiazide and ACE inhibitors has been described repeatedly over the past 7 years. Data on these types of tumors have been officially published not only in a number of large-scale european and american retrospective analyzes but also in the form of dozens of case studies with a retrospective/prospective nature. We describe the case of a patient who developed a basal cell carcinoma (BCC) of the chin, which enlarged significantly after taking potentially nitrosamine-contaminated metformin. The role of nitrosamines as a possible key factor in tumor development is discussed.

Keywords: Basal cell carcinoma. Drug-enhanced carcinogenesis. Metformin. Nitrosamines. Skin cancer. Valsartan.

Resumo

A contaminação potencial ou real de medicamentos amplamente distribuídos com nitrosaminas é atualmente um grave problema. Medicamentos como ranitidina, metformina, rifampicina, hidroclorotiazida, inibidores da ECA, sartans, usados em monoterapia ou em combinação com outras classes de medicamentos, contêm estes ingredientes que potencializam a geração e progressão tumoral. O dilema com o ˝aumento da disponibilidade das nitrosaminas diz respeito ao desenvolvimento subsequente não apenas de tumores de pele, mas também às vezes em combinação com outros tipos de tumores. O desenvolvimento, em particular, de tumores de queratinociticos aproximadamente após o mesmo período de tempo dentro da administração de fármacos como sartans, hidroclorotiazida e inibidores da ECA, não deve ser considerado surpreendente e foi descrito repetidamente nos últimos 7 anos. Os dados sobre esses tipos de tumores foram publicados oficialmente não apenas em várias análises retrospetivas europeias e americanas em larga escala, mas também na forma de dezenas de

***Corresponding author:**
Simona Kordeva
E-mail: simonakordeva97@gmail.com

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estudos de caso com natureza retrospetiva/prospetiva. Descrevemos o caso de um paciente que desenvolveu um carcinoma basocelular do mento que sofreu crescimento significativo após tomar metformina potencialmente contaminada com nitrosamina. Discute-se o papel das nitrosaminas como possível fator chave no desenvolvimento do tumor.

Palavras-chave: Nitrosaminas. Cancro de pele. Carcinoma basocelular. Carcinogénese mediada por fármacos. Metformina. Valsartan.

Introduction

The global problem of nitrosamines enhancing carcinogenesis has gained increasing importance in recent years[1]. In the scientific literature, there are additional new data on the contamination of commonly used medications by the presence of certain mutagens/carcinogens, also known as nitrosamines[2]. To all intents and purposes, metformin turns out to be one of this so-called ˝problematic drugs[3]˝

The amount of data in the medical literature postulates that both potential and actual contamination with nitrosamines is directly related to the development and progression of both melanocytic[4,5] and keratinocytic skin tumors[6,7], but in fact, not only[8].

Case report

A 61-year-old male (Fitzpatrick skin type 2) reported to the Dermatology Department with a growing cutaneous lesion on the face that was present for 20-25 years (as confirmed by the patient's picture ID card) but started growing progressively after initiating therapy in 2015. As the lesion wasn't considered cancerous or at risk for developing cancer, it was therefore left untreated. The patient denied a previous history of sunburns, allergies or any form of skin cancer in the family. Since 2015 he has been diagnosed with diabetes mellitus, hypercholesterolemia and hypertriglyceridemia. Systemic medications prescribed for type 2 diabetes were metformin hydrochloride 500 mg three times a day (2015-2017), dapagliflozin/metformin hydrochloride 5 mg/1000 mg twice daily (2017-2021) and glimepiride 4 mg twice daily in combination with metformin hydrochloride 1000 mg/day (2021-22). In 2015, after starting therapy, the lesion changed its shape, form and consistency over a short period of time and slowly progressed until the patient came for a dermatological evaluation in 2022.

Laboratory tests showed the following relevant abnormalities: glucose levels 8.77 mmol/L (normal 2.8-6.1 mmol/L), total cholesterol 5.54 mmol/L (normal < 5.17 mmol/L), HDL-cholesterol 1.09 mmol/L (normal for men > 1.45 mmol/L), LDL-cholesterol 4.20 mmol/L (normal < 3.36 mmol/L), VLDL-cholesterol 0.89 mmol/L (normal < 0.65 mmol/L), triglycerides 1.95 mmol/L (normal < 1.71 mmol/L), C-reactive protein (CRP) 8.36 mg/l (normal < 5 mg/L).

Dermatological examination showed a 4.5 cm ulcerated and infiltrated tumor lesion on the right lower facial area, at the level of the mandible (Fig. 1), with a deep central ulcer and elevated and uneven borders formed by pigmented and translucent nodules with telangiectasia, that was adherent to the deeper structures. Biopsy confirmed BCC.

Computed tomography scan of the head and neck showed a soft tissue tumor formation of about 80/17 mm with uneven outlines involving the skin and subcutaneous tissue at the level of the right mandible with no evidence of bone involvement. After contrast enhancement, the lesion significantly increased its density characteristic. No secondary or other focal pathological changes were seen in the brain parenchyma. A surgical approach, with a wide excision under local anesthesia, was recommended. The patient refused surgery, and radiation therapy is being considered.

Discussion

The role of nitrosamines has been discussed as a potential inducer of both melanocytic[9] and keratinocytic tumors[7]. In recent years, the regulatory authorities, in the face of EMA and FDA, have created new parameters/limits to help regulate/limit the availability of certain carcinogens/mutagens - nitrosamines, with the hope for maximum prevention for patients worldwide[10]. Nevertheless, because of the polymorbidity and the related multi-medication, the determination of the so-called acceptable daily intake doses for nitrosamines in a given drug gradually and increasingly loses its significance/relevance. Actually, the total concentration of nitrosamines taken by a given patient is most likely determined by the concentration or availability of nitrosamines in not one but several medications. The concomitant intake, for example, of thiazide diuretics with sartans, often turns out to have an additional risk in terms of developing skin cancer in combination with other forms of cancer[11,12], compared to monomedication with, for example, only a sartan[13].

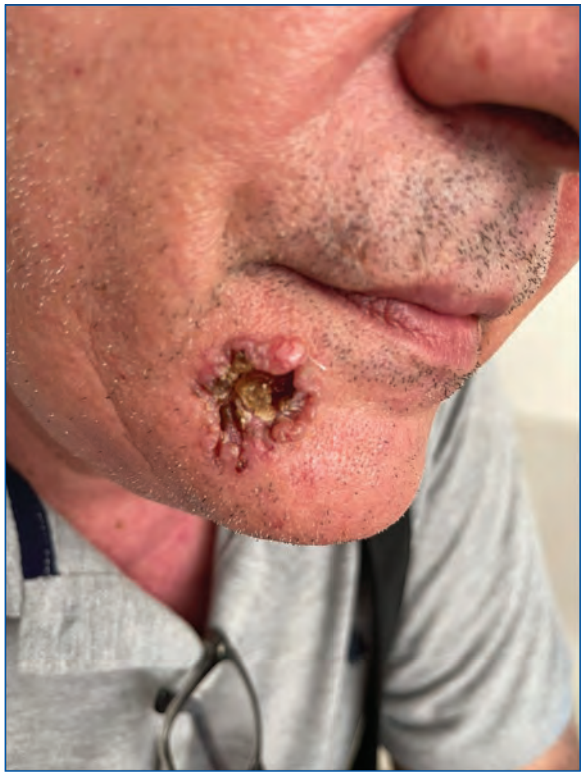

Figure 1. Large, ulcerated tumor lesion on the right lower facial area, at the level of the mandible, with 4-5 cm with elevated and uneven borders formed by some pigmented and translucent nodules with teleangiectasia typical of BCC, with deep ulceration in the middle with adherence to the deeper structures.

Therefore, the relationship between the intake of thiazide diuretics, metformin, rifampicin, or sartans, and the subsequent development of one or multiple cancers, should not be pathogenetically determined based on the individual action of each drug class, as mentioned substances have different mechanisms of action. A search for another pathogenetic inducer other than concepts such as "sporadicity" or "simple association" should then be looked after. This connection between the intake of these medications and the development of the same or relatively the same forms of cancer could be due to the availability of other substances or a contaminating substance that is available in many of the above-mentioned classes of drugs, particularly nitrosamines[14].

Keratinocyte tumors, such as basal cell and squamous cell carcinomas, were recently announced as a possible side effect of the treatment of hypertension with hydrochlorothiazide or with sartans/hydrochlorothiazide[15], well before companies such as Pfizer officially announced the presence of nitrosamine contamination in their products[16]. Therefore, side effects resulting from metformin contaminated with nitrosamines should also be analogous: both for the development of melanomas and keratinocytic skin tumors.

In the world literature, there is already data regarding the parallel administration of potentially contaminated metformin with sartans or metformin with sartans and hydrochlorothiazide, which led to the development of melanoma[5] or atypical fibroxanthoma in combination with prostate carcinoma[17].

The tumors that would arise as a result of such potential administration were similar to or analogous to the case presented, in which a previous skin lesion progressed into a large BCC in the chin area in a 61-year-old man after using potentially nitrosamine-contaminated metformin and other drugs seven years. In this case, we may suspect that nitrosamines in the drugs used might have enhanced BCC growth due to its known carcinogenic potential, but additional factors like ultraviolet exposure might also have contributed.

Key in terms of reasoning about the development of cancer after taking relevant medications should be, on the one hand[1], monitoring the dose-dependent time intervals in a larger group of patients and, on the other hand[2] regular control/identification regarding the type of the nitrosamines found in the batches of the medications. These two factors would contribute significantly to a further understanding of the real dimension of the effect of nitrosamines on enhanced cutaneous carcinogenesis.

Funding

None.

Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

References

1. Zmysłowski A, Książek I, Szterk A. N-nitrosodimethylamine contamination in the metformin finished products. Molecules 2020;25:5304.
2. Bharate SS. Critical analysis of drug product recalls due to nitrosamine impurities. J Med Chem 2021;64:2923–36.
3. Dharani S, Mohamed EM, Khuroo T, Ali HI, Reddy IK, Rahman Z, *et al*. In-use stability assessment of FDA approved metformin immediate release and extended release products for N-nitrosodimethylamine and dissolution quality attributes. Int J Pharm 2022;623:121923.
4. Tchernev G, Bitolska A, Patterson JW. Telmisartan (and/or nitrosamine) - induced occult melanoma: first reported case in world literature. Expert Rev Clin Pharmacol 2021;14:1075–80.
5. Tchernev G, Patterson JW. Telmisartan/hydrochlorothiazide-induced nevus-associated cutaneous melanoma: first report in the medical literature. Expert Rev Clin Pharmacol 2021;14:289–93.
6. Tchernev G, Oliveira N, Kandathil LJ, Patterson JW. Valsartan (and/or Nitrosamine) induced BCC and dysplastic Nevi: current insights. Clin Res Dermatol Open Access 2021;8:1–6.
7. Tchernev G, Poterov G, Patterson JW, Malev V. Sartans and cancer: multiple verrucous carcinomas and giant acral melanoma developing after antihypertensive therapy with valsartan and olmesartan. J Med Review (Bulgarian) 2020;56:58–60.
8. Tchernev G, Poterov G. Drug induced cancers: simultaneously development of cutaneous melanoma, colon carcinoma and Kaposi sarcoma under valsartan/hydrochlorothiazide. Clin Res Dermatol Open Access 2020;7:1–8.
9. Tchernev G, Kandathil LJ, Oliveira N. Insights into the development of lentigo maligna and dysplastic nevi: spotlight on the possible relation with sartans, thiazides and nitrosamines. J Port Soc Dermatol Venereol 2022;80:1–6.
10. https://www.ema.europa.eu/en/news/ema-finalises-opinion-presence-nitrosamines-medicines
11. Tchernev G, Temelkova I. Valsartan/hydrochlorothiazide induced prostate carcinoma in a patient who subsequently developed melanoma. J Biol Regul Homeost Agents 2019;33:1125–27.
12. Tchernev G, Poterov G. Antihypertensive drugs and cancer: simultaneously development of choroidal melanoma and colon carcinoma after administration with valsartan/hydrochlorothiazide. Clin Res Dermatol Open Access 2020;7:1–4.
13. Tchernev G, Poterov G, Malev V. Sartans and melanoma: valsartan induced multiple primary cutaneous melanomas: first description in the medical literature. Clin Res Dermatol Open Access 2020;7:1–3.
14. Tchernev G, Patterson JW, Malev V, Bitolska A, Batashki A, Cardoso JC, *et al*. Sartans, nitrosamines and melanoma development: the hidden truth! J Med Review (Bulgarian) 2021;57:36–7.
15. https://www.fda.gov/drugs/drug-safety-and-availability/fda-approves-label-changes-hydrochlorothiazide-describe-small-risk-non-melanoma-skin-cancer
16. https://www.pfizer.com/news/press-release/press-release-detail/pfizer-voluntary-nationwide-recall-lots-accuretictm
17. Tchernev G, Oliveira N, Kandathil LJ, Dimchova N, Terziev I, Patterson JW. Telmisartan and/ or nitrosamine induced prostate carcinoma and atypical fibroxanthoma: first report in world literature. J Med Review (Bulgarian) 2022;58: 65–7.

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IMAGES IN DERMATOLOGY

What's your diagnosis? A rare cutaneous benign tumor

Qual o seu diagnóstico? Um tumor cutâneo benigno raro

Ana G. Lopes[a], Maria J. Guimarães, Catarina Cerqueira, Joana Gomes, and Celeste Brito*

Dermatology Department of Hospital de Braga, Braga, Portugal
[a]ORCID: 0000-0003-1103-1075

Our case focuses on a 30-year-old female patient with no relevant priors.

The patient was referred to our dermatology department due to the appearance of a cutaneous lesion on the left leg during her last pregnancy which was 6 months ago.

At the dermatologic examination, she presented a macule with brown pigment on the center and an erythematous halo, well-demarcated, with superficial scaling, < 1 cm in diameter, and on the anterior surface of the left leg (Figure 1).

Dermoscopy revealed light brown dots and globules on a yellow background, with dotted vessels and white streaks at the periphery (Figure 2).

A cutaneous biopsy showed acanthosis with mild orthokeratotic hyperkeratosis, larger than usual keratinocytes, and hyperpigmentation of the basal layer. The histopathological findings were compatible with a large cell acanthoma (LCA).

An LCA is a rare epidermal benign tumor, considered by some a variant of the solar lentigo with cellular hypertrophy. It occurs most frequently in women, older

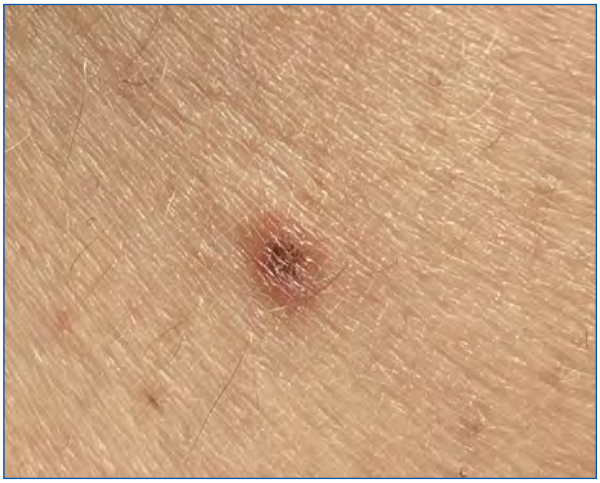

Figure 1. Macule with brown pigment on the center and an erythematous halo, well-demarcated, with superficial scaling, < 1 cm in diameter, and on the anterior surface of the left leg.

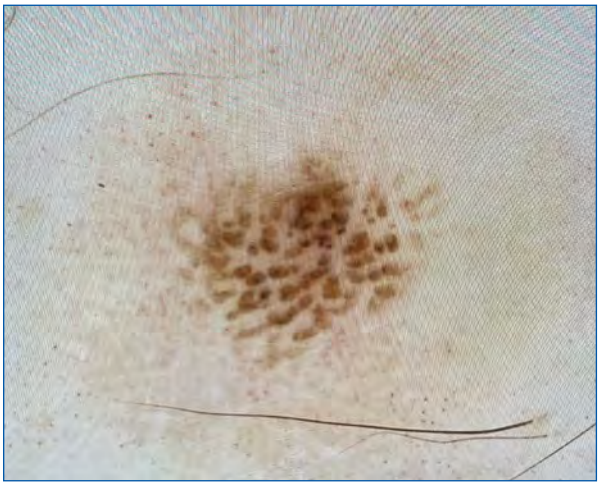

Figure 2. Dermoscopy of the lesion, showing light brown dots and globules on a yellow background, with dotted vessels, and white streaks at the periphery.

***Corresponding author:**
Ana G. Lopes
E-mail: anagabri2@gmail.com

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people, and in sun-exposed sites, such as the face and extremities[1,2]. Clinically, LCA may be difficult to be differentiated from a solar lentigo, a pigmented actinic keratosis, or a flat seborrheic keratosis[3]. A recently published study performed on 33 lesions (26 patients) identified distinct dermoscopic findings of LCA[4]. The most frequent dermoscopic findings are a yellow opaque homogenous area, grey/brown dots and globules, a moth-eaten border, white streaks, and a pseudonetwork[2,4], most of which were also present in this case. Another study evaluated 13 patients and also identified these as the most frequent dermoscopic features and found that milia-like cysts and white to yellow surface scale were uncommon findings[5].

Therefore, dermoscopy is a noninvasive tool that can significantly aid in the diagnosis of LCA.

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Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article.

References

1. Mehregan DR, Hamzavi F, Brown K. Large cell acanthoma. Int J Dermatol. 2003;42:36–9.
2. Fraga GR, Amin SM. Large cell acanthoma: a variant of solar lentigo with cellular hypertrophy. J Cutan Pathol. 2014;41:733–9.
3. Patsatsi A, Lazaridou E, Fotiadou C, Kyriakou A, Sotiriadis D. Large cell acanthoma: a debate throughout the decades. Dermatol Pract Concept. 2014;4:43–5.
4. Jung JH, Jeong SM, Kwon DI,Seong SH, Jang JY, Kim JH, *et al*. Dermoscopic findings and histopathological correlation in large cell acanthoma. Australas J Dermatol. 2022;63:e340–4.
5. Park JB, Jung JH, Kwon DI, Seong SH, Suh KS, Jang MS, *et al*. Dermoscopic features of large cell acanthoma. J Am Acad Dermatol. 2021;85:AB52

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LETTER TO EDITOR

Erythema multiforme caused by topical imiquimod 3.75%

Eritema multiforme causado por imiquimod tópico 3.75%

César Magalhães[1,a], André Coelho[2], Miguel Costa[1], and Nuno Menezes[1]*

[1]Dermatology Service, Centro Hospitalar Vila Nova de Gaia/Espinho; [2]Pathological Anatomy Laboratory, Unilabs, Porto, Portugal
[a]ORCID: 0000-0002-3986-6253

Imiquimod, 3.75% cream, is a topical immunomodulator approved for treating actinic keratoses. Although local side effects are more frequent, it can also have systemic side effects. We report that imiquimod 3.75% can also produce erythema multiforme (EM), thus discarding it as an alternative to imiquimod 5% on this adverse effect.

An 81-year-old man, with a history of squamous cell carcinoma, presented with actinic damage and several actinic keratoses on the nose, cheeks, and frontal area. Treatment with imiquimod 3.75% was prescribed for all actinic keratoses to be applied once daily for two treatment cycles of 2 weeks, spaced by 2 weeks. In the 2nd week of the second cycle, the patient initiated an intense local reaction at the sites of application associated with erythematous lesions on the upper body, arms, and legs. Treatment was suspended. Physical examination revealed extensive areas of exudative and crusting lesions across the whole face (Figure 1A) and several round erythematous papules, in the central upper chest area, on the extensor surfaces of the forearms and lower legs, and the dorsum of the hands; some of these papules had central vesiculation or erosion, and others had a target morphology (Figure 1B). Mucosae, palms, or soles were not involved. The patient did not report a previous infection and was not taking any drugs other than his usual medication. Biopsy of a target lesion revealed abundant apoptotic keratinocytes, hydropic degeneration of the basal cell layer with band-like infiltration of leukocytes, and a slight perivascular lymphoid infiltrate in the papillary dermis, all consistent with EM (Figure 1C). Treatment with imiquimod was suspended. We initiated prednisone (30 mg) for 2 weeks and treated the face lesions with topical antibiotics. Treatment was effective, with complete clearance of the symptoms and cutaneous alterations within 3 weeks, and the diagnosis of EM induced by imiquimod was established.

Imiquimod is a topical immunomodulator with antitumoral and antiviral activity approved for treating actinic keratoses. It stimulates innate and acquired immune responses by promoting the secretion of pro-inflammatory and antimicrobial cytokines leading to a T-helper 1 response and thus destroying tumors and virus-infected cells[1]. Although local side effects are more frequent, it can also have systemic side effects. We report that imiquimod 3.75% can also produce erythema multiforme, thus discarding it as an alternative to imiquimod 5% on this adverse effect.

The majority of imiquimod local side effects include erythema, crusting, and ulceration, frequently observed in the application area, which resolves satisfactorily on drug withdrawal. EM and other systemic eruptions were already described in patients under topical imiquimod. Many systemic drugs are associated with EM (nonsteroidal anti-inflammatory drugs, sulfonamides,

***Corresponding author:**
César Magalhães
E-mail: cfsmagalhaes@gmail.com

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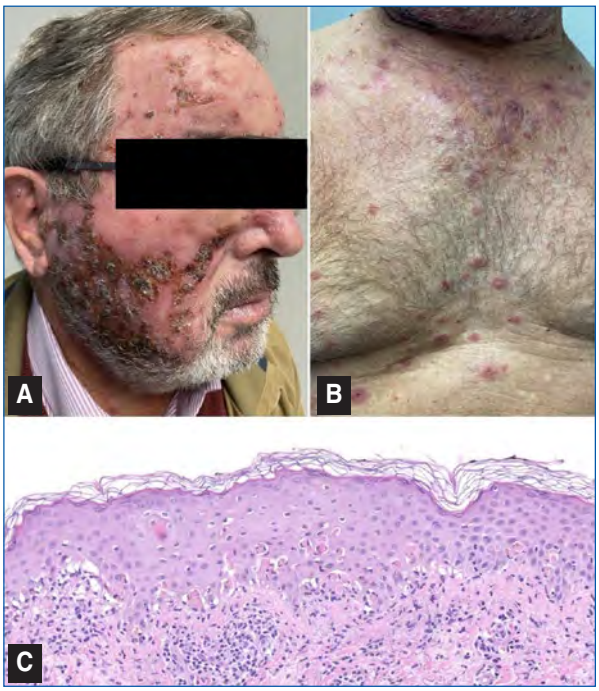

Figure 1. A: face, showing exudative and crusting lesions. **B:** anterior trunk, revealing target lesions. **C:** abundant apoptotic keratinocytes, hydropic degeneration of the basal cell layer with band-like infiltration of leukocytes, and a slight perivascular lymphoid infiltrate in the papillary dermis (HE 200x).

anticonvulsants, and allopurinol), but few with topical treatments[1–3]. We found under 10 cases of EM associated with topical imiquimod, all with imiquimod 5%. This reaction is probably due to disproportionated systemic absorption and imiquimod immunomodulatory effects triggering a hypersensitivity reaction (type III or IV)[2]. An intense local inflammatory response to imiquimod, such as that experienced by our patient, was already proposed as a potential risk factor for systemic absorption, predisposing patients to EM[3].

We conclude that despite its lower concentration, the 3.75% formulation can also induce EM-like eruptions, thus not being a valuable alternative to those who experience this reaction on the 5% formulation. This also supports an immunologically mediated mechanism of drug reaction. All previously reported cases with 5% imiquimod were in a heterogeneous group of patients, and it does not appear to be a consistent finding that could increase immunoreactivity (e.g., cancer). Genetic predisposition may be the driving factor, so studies on the human leukocyte antigens alleles could also be critical in finding predisposed patients.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

References

1. García-Arpa M, Rodríguez-Vázquez M, Delgado Portela M, Vera Iglesias E. Erythema multiforme due to 5% imiquimod cream. Actas Dermosifiliogr. 2010;101:551–2.
2. Peña-López S, Suárez-Magdalena O, Monteagudo B, Cabanillas M. Erythema multiforme caused by treatment with topical imiquimod 5% in a patient with Gorlin syndrome. Actas Dermosifiliogr. 2018;109:277–8.
3. Ballester I, Guijarro J, Silvestre JF, Niveiro M. Erythema multiforme induced by imiquimod 5% cream. Int J Dermatol. 2014;53:e347–8.