JAKUBOWSKA, Wiktoria, PISERA, Piotr, KIEŁKOWICZ, Aleksandra, PACTWA, Filip, POPIŃSKA, Zuzanna, ŚLUSARCZYK, Daniel, ŻMUDA, Bartłomiej and ŻUBEREK, Michał. From pathogenesis to current treatment of the cutaneous psoriasis - a literature review, Journal of Education, Health and Sport. 2023;49(1):56-70. eISSN 2391-8306. https://dx.doi.org/10.12775/JEHS.2023.49.01.004 https://apcz.umk.pl/JEHS/article/view/47541 https://zenodo.org/records/10439561

From pathogenesis to current treatment of the cutaneous psoriasis - a literature review

Wiktoria Jakubowska, Medical University of Lodz, al. Tadeusza Kościuszki 4, 90-419 Łódź,

Poland

https://orcid.org/0009-0008-9290-503X, wiktoria.jakubowska@stud.umed.lodz.pl

Piotr Pisera, Faculty of Medicine, Medical University of Lodz, al. Tadeusza Kościuszki 4, 90-

419 Łódź, Poland

https://orcid.org/0009-0002-7086-7307, ptrpsr5@gmail.com

Aleksandra Kielkowicz, Central Clinical Hospital of Medical University of Lodz, ul. Pomorska 251, 92-213 Łódź, Poland

https://orcid.org/0009-0003-7837-0925, aleksandra.kielkowicz@gmail.com

Filip Pactwa, Faculty of Medicine, Medical University of Lodz, al. Tadeusza Kościuszki 4, 90-419 Łódź, Poland

https://orcid.org/0000-0002-9559-5072, filip.pactwa@onet.pl

Zuzanna Popińska, Faculty of Medicine, Comenius University Bratislava Špitálska 24, 813-72 Bratislava, Slovakia https://orcid.org/0000-0002-8224-6770, Zuzpopinska@gmail.com

The journal has had 40 points in Ministry of Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science 60.3.11.2023 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Health Sciences (Field of medical and health sciences); Medical sciences (Field of medical and health sciences); Socio-economic geography and spatial management (Field of social sciences); Fedagogy (Field of social sciences); Earth and Environmental Sciences (Field of exect and natural sciences); Socio-economic geography and spatial management (Field of social sciences); Fedagogy (Field of social sciences); Earth and Environmental Sciences (Field of exect and natural sciences); Aution antatra sciences); Nultiverse 2019 - aktualay rok 40 punktów. Załącznik do komunikatu Ministra Edukacji i Nauki z dnia 03.11.2023 Lp. 32318. Posiada Unikatowy Identyffkator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki medyczne (Dziedzina nauk medycznych) i nauk o zdrowiu); Nauki medyczne (Dziedzina nauk nedycznych) i nauk o zdrowiu; Geografia spolezno-ekonomiczna i gospodarka przestrzenna (Dziedzina nauk spoleznych); Pedagogika (Dziedzina nauk spolezzych); Nauki o Ziemi i środowisku (Dziedzina nauk stowe; Paryrofiniczych). O The Authors 2023; This article is distributed under the terns of the Creative Commons Attribution Non commercial License which permits any noncommercial license Share alike. (http://creativecommons.org/filenses/by-nes/s4/0) which permits medication of this paper. The authors declare that there is no conflict of interests regarding the publication of this paper. Received: 12.12.2023. Revised: 26.12.2023. Accepted: 27.12.2023. Published: 30.12.2023.

Daniel Ślusarczyk, Military Medical Academy Memorial Teaching Hospital – Central Veterans' Hospital, ul. Stefana Żeromskiego 113, 90-549 Łódź, Poland https://orcid.org/0009-0000-3338-976X, dslusarczyk98@gmail.com

Bartlomiej Żmuda, Norbert Barlicki Memorial Teaching Hospital No.1 of the Medical University of Lodz, ul. Dr. Stefana Kopcińskiego 22, 90-153 Łódź, Poland https://orcid.org/0009-0005-6290-0455, zmudabartek98@gmail.com

Michał Żuberek, Faculty of Medicine Nicolaus Copernicus University in Torun, Collegium Medicum in Bydgoszcz, ul. Jagiellonska 13, 85-067 Bydgoszcz, Poland https://orcid.org/0009-0008-2358-6784, zuberekmichal99@gmail.com

Corresponding author:

Wiktoria Jakubowska Medical University of Lodz, al. Tadeusza Kościuszki 4, 90-419 Łódź, Poland +48 516 151 408 wiktoria.jakubowska@stud.umed.lodz.pl

Abstract

Introduction:

Psoriasis is a chronic inflammatory autoimmune disease that can be divided into several subtypes based on the areas of the body occupied by the lesions and the severity of the disease. The overall prevalence of psoriasis ranges from 0 to 11,8%. The disease occurs with equal frequency in both sexes. PsO cannot be completely cured, so many patients experience stigma and have diminished self-esteem due to the characteristic appearance of the lesions.

Aim of the study:

The purpose of the study is to summarize the available knowledge about classification and options for psoriasis treatment. The options in diagnosis and treatment, including the latest methods, were described and summarized.

Materials and methods:

Literature available in the PubMed database was reviewed using the following keywords: "Psoriasis", "Nail Psoriasis", "Psoriasis Vulgaris", "Psoriasis Treatment", "New Psoriasis Treatment", "Psoriasis Classification", "Biologic Therapy for Psoriasis", "Systemic Therapy for psoriasis".

Conclusions:

Psoriasis is a genetic skin condition mediated by the immune system. The underlying mechanisms entail intricate interactions between the innate and adaptive immune system. There are various indices for assessing the severity of psoriasis, the most commonly used of which is PASI(Psoriasis Area and Severity Index). Retinoids, cyclosporine and methotrexate are the non-biologic therapies most frequently employed for moderate to severe psoriasis treatment, while topical therapy, which includes mainly corticosteroids and vitamin D analogues, is a successful approach for effectively managing mild psoriasis.

Keywords: Psoriasis; Therapeutics

Introduction

Psoriasis is a chronic, recurring, inflammatory skin disease in which genetic predisposition is very strong. The worldwide incidence is about 2%, but varies according to regions[1]. The disease is characterized by presence of scaly, erythematous plaques - the effect of epidermal cell hyperplasia. The epidemiology distinguishes 2 peaks of incidence: first - around age 20, second - around age 60. Auspitz's sign and oil stain symptom are patognomonic for psoriasis. About 36% of individuals diagnosed with psoriasis possess a familial background of the condition, and several genetic susceptibility loci have been recognized[2][3].

The purpose of the study is to summarize the available knowledge about classification and therapeutic options for psoriasis treatment. The options in diagnosis and treatment, including the latest methods, were described and summarized.

Pathogenesis

Psoriasis is a complex disease with a multigene and multifactorial inheritance pattern. Many genes, presented on different chromosomes, are responsible for the manifestation of psoriasis and the most important role in susceptibility to early psoriasis is played by allele HLA-Cw*06 located in PSORS1- region of chromosome 6. The formation of psoriatic plaque is conditioned by an abnormal hereditary and acquired immune response, which is mediated by T lymphocytes. Activation of Th1 and Th17 lymphocytes plays an important role in the formation and maintenance of psoriatic lesions. Th1 lymphocytes produce IL-2, IL-3, TNF, IL-12 and gamma interferon, while Th17 lymphocytes secrete IL-17 and IL-22 - cytokines that stimulate proliferation of keratinocytes. The role of T lymphocytes in the pathogenesis of psoriasis leaves no doubt, but the factor or event that triggers their activation is still unknown. Streptococcal superantigens may have a key role in the initiation of autoimmune response, but these are only speculations. The clinical manifestation of psoriasis among people with a genetic predisposition is influenced by well-studied environmental factors, such as: physical injuries, infections, emotional stress and some medicaments(ACE-I, beta-blockers, lithium)[4][5].

Main symptoms and predilection sites

The primary lesion characteristic for psoriasis is a papule. Papules form larger foci, so-called psoriatic plaques that can involve any body part, but the most common sites of psoriasis are: hairy scalp, navel area, sacrococcygeal region, extensor surfaces of elbows and knees and nails. Clinical features that facilitate the diagnosis of psoriasis are mainly:

Auspitz's sign - punctate bleeding of psoriatic papule caused by mechanical removal of scales candle sign - removal of scales shows shiny, stearin-like surface

Köbner's phenomenon - characteristic symptom of active psoriasis (not present in remission); about 8-14 days after minor trauma, such as scratch, there is a formation of psoriatic lesions in the damaged area[6].

Classification

In scientific literature, the terms psoriasis and psoriasis vulgaris are often used interchangeably. However, it's essential to note that there are significant differences among various clinical subtypes. Psoriasis vulgaris, the most prevalent phenotype, impacts approximately 85–90% of individuals diagnosed with psoriasis [7][8]. Increasing evidence indicates that patients with psoriasis, in contrast to the general population, have a higher incidence of various chronic and severe health diseases. These include metabolic disorders, diabetes, arthritis, hypertension, cardiovascular diseases, anxiety or depression, Crohn's disease, and lymphoma, as well as other cancers[8][9].

We can distinguish the following types of cutaneous psoriasis:

Psoriasis Vulgaris, also known as Plaque Psoriasis - the most common type, typical manifestations of plaque psoriasis involve erythematous and clearly defined pruritic plaques covered in silvery scales[9]. The plaques may merge and extend to encompass extensive skin areas[10]. Within plaque psoriasis we can differentiate scalp and nail psoriasis. Manifestations of scalp psoriasis vary from mild, erythematous and scaly plaques to complete coverage of the scalp - typically, this extends beyond the hairline, creating the impression of clustered or bundled hair[11]. When it comes to nail psoriasis, approximately 40-50% of patients with PsO present psoriatic nail disease, and the lifetime occurrence of nail PsO (NP) can be as high as 90%[12]. Nail psoriasis is primarily characterized by the presence of nail pits, with additional manifestations such as discoloration resembling oil drops, splinter hemorrhages in the nail bed, and the deterioration or loosening of the nail plate. Importantly, it serves as a significant indicator for the development of psoriatic arthritis (PsA)[13]. The presence of nail issues is linked to increased severity of Psoriasis (PsO) and is more prevalent among individuals with joint complications. NP is additionally correlated with a reduced quality of life (QOL) in individuals with PsO and/or Psoriatic Arthritis (PsA). It can lead to significant pain and is linked to a higher incidence of anxiety or depression[14]. Patients with Nail Psoriasis (NP) frequently encounter challenges when trying to put on socks or shoes and face difficulties in carrying out daily household tasks, such as dishwashing or vacuuming. This difficulty contributes to a decline in health-related quality of life (QOL) and a decrease in work productivity.

Inverse Psoriasis(IP), also known as **flexural** or **intertriginous psoriasis** - typical especially in infants, including involvement of the diaper region resulting in the formation of "napkin psoriasis"[15]. Frequently, there are superficial erosions and maceration, leading to increased itching and discomfort from perspiration[16]. IP is clinically characterized by smooth, moist, well demarcated, scaly-less erythematous patches. Folds of rubbing areas, such as the inguinal folds are the most frequently impacted areas, also followed by axillaes, perianal region, umbilicus and retroauricular areas(hip groove, groin, armpit and region under the breast). Additionally, the antecubital and popliteal fossae, as well as interdigital spaces, may also experience involvement. In IP, superinfection by bacteria and fungi, particularly Candida spp, is common due to the favorable environment for microorganism growth created by the moist skin. Conversely, colonization of flexural areas may also increase the likelihood of IP lesions presence[17].

Pustular Psoriasis - skin disorder identified by yellowish, multiple and sterile pustules on a reddened base, exhibiting diverse clinical presentations and distribution patterns. Pustular psoriasis can be categorized into subtypes according to its clinical manifestation and the location of pustules. We can divide pustular psoriasis into 2 subtypes: localized and generalized. Localized pustular psoriasis encompasses palmoplantar pustulosis (PPP) and acrodermatitis continua of Hallopeau (ACH). Generalized pustular psoriasis is an autoinflammatory skin condition marked by sterile pustules, with or without a background of plaque psoriasis history[18]. GPP typically manifests acutely on existing psoriatic lesions or unaffected skin, often accompanied by systemic inflammation[19]. Acute GPP commonly conditions experience of systemic symptoms including chills, fever, general malaise, loss of appetite, intense pain and nausea. Additional manifestations may include geographic tongue, thickening of nail plates and pustules beneath the nails[20]. Without proper treatment, acute GPP has the potential to result in mortality due to concurrent infections and the failure of multiple systemic functions. Palmoplantar pustulosis is an uncommon and recurrent inflammatory condition impacting the palms and/or soles. It is characterized by sterile, symmetrically arranged pustules that emerge on a background of erythematous and scaly skin. It may endure for extended periods and typically proves resistant to treatment, marked by intervals of partial or complete remission interspersed with recurring flare-ups [21].

ACH presents with pustules and erythema beneath on the fingertip, occasionally on the toe [22]. Nails are consistently affected in ACH; if there is no nail participation, alternative diagnoses, including PPP, should be taken into consideration[23].

Guttate Psoriasis - a form of psoriasis typically induced by group-A streptococcal infection(either in the throat or perianal region), more prevalent in children and adolescents than in adults. Individuals exhibit numerous small lesions resembling drops, which are effectively treated with topical and phototherapies[24]. Approximately one-third of patients diagnosed with guttate psoriasis will go on to develop plaque psoriasis during their adulthood.

Erythrodermic psoriasis - rare variant of psoriasis that is clinically characterized by significant inflammation and scaling, involving a minimum of 75–90% of the body surface area (BSA)[25][26]. Erythrodermic psoriasis is accompanied by systemic symptoms including fever, chills, dehydration, lymphadenopathy, gastrointestinal discomfort and cachexia[27].

Treatment

Psoriasis is a chronic disease, so it demands a long-term therapy. The selection of treatment for psoriasis is influenced mainly by the severity of the disease and the presence of any comorbid conditions, but price of the drug also plays an important role. Patients with psoriasis are often classified into two groups: those with mild psoriasis and those with moderate to severe psoriasis. This categorization is based on the clinical severity of the lesions, the extent of affected body surface area and the impact on the patient's quality of life[28]. Mild psoriasis is defined as $BSA \le 10$, $PASI \le 10$ and $DLQI \le 10$, while moderate to severe psoriasis are defined as BSA > 10 or PASI > 10 and DLQI > 10. Mild psoriasis can be effectively treated using topical therapy, which includes:

corticosteroids vitamin D analogues calcineurin inhibitors retinoids dithranol in increasing concentrations phototherapy - PUVA, UVB-311(311nm) and wide-range UVB(280-320nm) Systemic treatment is typically necessary for moderate to severe psoriasis. The consideration of comorbidities, such as psoriatic arthritis, is also crucial in determining the appropriate treatment. In order to clearly summarize the available methods of systemic treatment, they will

be divided into 2 groups: oral systemic therapy and biologic therapy.

Oral Systemic Therapy

Retinoids - natural or synthetic molecules related to vitamin A. Retinoids promote the differentiation of keratinocytes and decrease epidermal hyperplasia, resulting in a deceleration of cell replication[29]. Acitretin, an active metabolite of etretinate, is the main retinoid used in psoriasis treatment. Acitretin is prescribed at a daily dose ranging from 0,3 to 0,5 mg/kg of

body weight, with the maximum allowable dosage being 1 mg/kg of body weight per day. Dose-dependent cheilitis is the most prevalent side effect observed in all patients.

Methotrexate(MTX) - an analogue of folic acid that inhibits dihydrofolate reductase, as well as DNA synthesis. The initial suggested dosage of 7,5–10 mg per week can be raised to a maximum of 25 mg per week[30][31]. A low dosage of MTX might exhibit anti-inflammatory effects by elevating adenosine levels and influencing immune cells[32]. The most prevalent side effects include nausea, abnormally high level of liver transaminase, leucopenia and vomiting.

Cyclosporine A(CyA) - a calcineurin inhibitor. Cyclosporine proves effective in inducing remission in psoriasis and serves as a maintenance therapy for a duration of up to two years[33]. Cyclosporine is utilized as a short-term, intermittent therapy with a dosage ranging from 2.5 to 5.0 mg/kg of body weight, administered for a period of 10 to 16 weeks. The possible side effects are hepatic and renal toxicity, elevated blood pressure, heightened susceptibility to infections, an increased risk of lymphoma and non-melanoma skin cancer[34]. On nail psoriasis, CyA is more effective than etretinate.

Apremilast - a selective phosphodiesterase-4 inhibitor. PDE4 serves as the primary enzyme in immune cells like macrophages, T cells and epithelial cells. By blocking the enzyme, apremilast decreases the production of pro-inflammatory cytokines such as TNF- α , IFN- γ , IL-12 and elevates IL-10 levels. At week 16, apremilast demonstrated a 33.1% PASI 75 response. The primary side effects include diarrhea, vomiting and depressive symptoms - they are typically not life-threatening but may be significant enough to justify discontinuation[35].

Biologic Therapy

TNF α **Inhibitors** - they have been accessible for more than ten years and prove effective in treating both plaque psoriasis and psoriatic arthritis. At present, there are four drugs within this classification: etanercept, infliximab, adalimumab and certolizumab. Etanercept stands out among biologics as it differs from monoclonal antibodies, being instead a recombinant human fusion protein. Infliximab is a chimeric monoclonal antibody of the IgG1 subtype. At the 10-week mark, PASI 75 response with a 5 mg/kg dose of infliximab were 80%[36]. Certolizumab

pegol is a pegylated Fab' fragment derived from a humanized monoclonal antibody targeting TNF- α . It is sanctioned for utilization during pregnancy and lactation.

IL-17 Inhibitors - IL-17, the main cytokine produced by T-helper 17 cells, plays a significant role in the development of inflammatory skin conditions. At present, secukinumab, ixekizumab and brodalumab are available for psoriasis treatment as inhibitors of IL-17. Secukinumab and ixekizumab inhibit IL-17A, while brodalumab targets the IL-17 receptor. Common side effects induced by using this group of drugs include nasopharyngitis, upper respiratory tract infection, headache and arthralgia. Candida infections occur more frequently in individuals treated with anti-IL17 biologics like secukinumab and ixekizumab, in comparison to those receiving etanercept[37]. In patients with psoriasis who also have Crohn's disease the use of anti-IL-17 biologics should be avoided.

IL-23 and IL-23/IL-12 Inhibitors-IL-23 is a dimeric structure consisting of p40 and p19 subunits. At present, ustekinumab, guselkumab, risankizumab and tildrakizumab are accessible for psoriasis treatment as IL-23 inhibitors. The initial biologic sanctioned for psoriasis vulgaris treatment - after TNF- α inhibitors - was ustekinumab, a monoclonal antibody targeting the p40 subunit of IL-23 and IL-12. Ustekinumab is also beneficial in managing PsA and Crohn's disease. It is offered in two doses, 45 mg and 90 mg. Infections are among the severe adverse effects mentioned in the label of ustekinumab. Guselkumab, risankizumab and tildrakizumab are fully human monoclonal antibodies with specificity for the p19 subunit.

Conclusions

Psoriasis is a chronic inflammatory skin disease clinically manifested by erythematous, welldemarcated skin lesions covered with adherent scales. There is a number of clinical features that facilitate the diagnosis of psoriasis, such as Auspitz's sign and Köbner's phenomenon. There are several forms of the disease depending on the predominant lesions and their location, but the most common type is psoriasis vulgaris. Topical treatment is designed for the majority of psoriasis patients with limited disease and consists of exfoliating drugs in the first stage, then anti-inflammatory and keratosis-regulating drugs once the scales are removed. Systemic treatment, which includes oral systemic therapy and biologic therapy, should be used in moderate to severe psoriasis. Moreover, psoriasis should not be treated with systemic corticosteroids, which, on the one hand, have an anti-inflammatory effect and can cause the rapid resolution of lesions, but on the other hand induce a high risk of psoriasis recurrence in its most severe forms.

Supplementary materials

Not applicable

Author's contribution

Conceptualization, Wiktoria Jakubowska and Piotr Pisera; methodology, Wiktoria Jakubowska and Daniel Ślusarczyk; software, Piotr Pisera and Aleksandra Kiełkowicz; check, Filip Pactwa and Aleksandra Kiełkowicz; formal analysis, Zuzanna Popińska and Daniel Ślusarczyk; investigation, Bartłomiej Żmuda and Michał Żuberek; resources, Michał Żuberek and Wiktoria Jakubowska; data curation, Bartłomiej Żmuda and Zuzanna Popińska; writing - rough preparation, Wiktoria Jakubowska; writing - review and editing, Wiktoria Jakubowska and Bartłomiej Żmuda; visualization, Daniel Ślusarczyk and Filip Pactwa; supervision, Michał Żuberek and Filip Pactwa; project administration, Wiktoria Jakubowska. All authors have read and agreed with the published version of the manuscript.

Funding Statement

The study did not receive special funding.

Institutional Review Board Statement

Not applicable

Informed Consent Statement

Not applicable

Data Availability Statement

The data presented in this study is available upon request from the correspondent author.

Acknowledgments

Not applicable

Conflict of Interest Statement

The authors report no conflict of interest.

List of references:

 Christophers E. Psoriasis—Epidemiology and clinical spectrum. Clin. Exp. Dermatol. 2001;26:314–320

https://doi.org/10.1046/j.1365-2230.2001.00832.x

- Elder JT. Genome-wide association scan yields new insights into the immunopathogenesis of psoriasis. Genes Immun. 2009;10:201–9 <u>https://doi.org/10.1038/gene.2009.11</u>
- Elder JT, Bruce AT, Gudjonsson JE, Johnston A, Stuart PE, Tejasvi T, et al. Molecular dissection of psoriasis: integrating genetics and biology. J Investigat Dermatol. 2010;130:1213–26

https://doi.org/10.1038/jid.2009.319

- Griffiths CE, Christophers E, Barker JN. A classification of psoriasis vulgaris according to phenotype. Br. J. Dermatol. 2007;156(2): 258-262 <u>https://doi.org/10.1111/j.1365-2133.2006.07675.x</u>
- Chandran V, Raychaudhuri SP. Geoepidemiology and environmental factors of psoriasis and psoriatic arthritis. J. Autoimmun. 2010; 34(3):314-321 <u>https://doi.org/10.1016/j.jaut.2009.12.001</u>
- Raychaudhuri SK, Maverakis E, Raychaudhuri SP. Diagnosis and classification of psoriasis. Autoimmun. Rev. 2014;13(4-5): 490-495
 https://doi.org/10.1016/j.autrev.2014.01.008
- Lowes MA, Bowcock AM, Krueger JG. Pathogenesis and therapy of psoriasis. Nature. 2007;445:866–73

https://doi.org/10.1038/nature05663

- Barker JN. Pathogenesis and clinical features of psoriasis. Lancet. 2007;370:263–71 https://doi.org/10.1016/S0140-6736(07)61128-3
- Nestle FO, Kaplan DH, Barker J. Mechanisms of disease: psoriasis. New Engl J Med. 2009;361:496–509

https://doi.org/10.1056/NEJMra0804595

 Ortonne J, Chimenti S, Luger T, Puig L, Reid F, Trueb RM. Scalp psoriasis: European consensus on grading and treatment algorithm. J. Eur. Acad. Dermatol. Venereol. 2009;23:1435–1444 https://doi.org/10.1111/j.1468-3083.2009.03372.x

- 11. Boehncke WH, Schon MP. Psoriasis. Lancet. 2015;386:983–94 https://doi.org/10.1016/S0140-6736(14)61909-7
- Armesto S, Esteve A, Coto-Segura P, Drake M, Galache C, Martínez-Borra J, et al. Nail psoriasis in individuals with psoriasis vulgaris: a study of 661 patients. Actas Dermosifiliogr. 2011;102:365-72

https://doi.org/10.1016/j.ad.2011.02.007

 Kaeley GS, Eder L, Aydin SZ, Rich P, Bakewell CJ. Nail psoriasis: diagnosis, assessment, treatment options, and unmet clinical needs. J Rheumatol. 2021;48:1208– 20

https://doi.org/10.3899/jrheum.201471

- 14. Sobolewski P, Walecka I, Dopytalska K. Nail involvement in psoriatic arthritis. Rheumathology. 2017;55:131-5 https://doi.org/10.5114/reum.2017.68912
- 15. Bronckers IM, Paller AS, van Geel MJ, van de Kerkhof PC, Seyger MM. Psoriasis in children and adolescents: diagnosis, management and comorbidities. Paediatr Drugs. 2015;17(5):373–384 https://doi.org/10.1007/s40272-015-0137-1
- Merola JF, Qureshi A, Husni ME. Underdiagnosed and undertreated psoriasis: nuances of treating psoriasis affecting the scalp, face, intertriginous areas, genitals, hands, feet, and nails. Dermatol Ther. 2018;31(3):e12589
 https://doi.org/10.1111/dth.2018.31.issue-3
- 17. Omland SH, Gniadecki R. Psoriasis inversa: a separate identity or a variant of psoriasis vulgaris?
 Clin Dermatol. 2015;33(4):456–461
 https://doi.org/10.1016/j.clindermatol.2015.04.007
- 18. Choon SE, Lebwohl MG, Marrakchi S, Burden AD, Tsai TF, Morita A, et al. Study protocol of the global Effisayil 1 Phase II, multicentre, randomised, double-blind, placebo-controlled trial of spesolimab in patients with generalized pustular psoriasis presenting with an acute flare. BMJ Open. 2021;11:e043666 <u>https://doi.org/10.1136/bmjopen-2020-043666</u>

- Hoegler KM, John AM, Handler MZ, Schwartz RA. Generalized pustular psoriasis: a review and update on treatment. J Eur Acad Dermatol Venereol. 2018; 32:1645–51 <u>https://doi.org/10.1111/jdv.14949</u>
- Robinson A, Van Voorhees AS, Hsu S, Korman NJ, Lebwohl MG, Bebo BF, et al. Treatment of pustular psoriasis: from the Medical Board of the National Psoriasis Foundation. J Am Acad Dermatol. 2012;67:279–88 <u>https://doi.org/10.1016/j.jaad.2011.01.032</u>
- 21. Freitas E, Rodrigues MA, Torres T. Diagnosis, screening and treatment of Patients with Palmoplantar Pustulosis (PPP): a review of current practices and recommendations. Clin Cosmet Investig Dermatol. 2020;13:561–78 https://doi.org/10.2147/CCID.S240607
- Smith MP, Ly K, Thibodeaux Q, Bhutani T, Liao W, Beck KM. Acrodermatitis continua of Hallopeau: clinical perspectives. Psoriasis. 2019;9:65–72 <u>https://doi.org/10.2147/PTT.S180608</u>
- Navarini AA, Burden AD, Capon F, Mrowietz U, Puig L, Köks S, et al. European consensus statement on phenotypes of pustular psoriasis. J Eur Acad Dermatol Venereol. 2017;31:1792–9

https://doi.org/10.1111/jdv.14386

 Dupire G, Droitcourt C, Hughes C, Le Cleach L. Antistreptococcal interventions for guttate and chronic plaque psoriasis. Cochrane Database Syst Rev. 2019 Mar 05;3(3):CD011571

https://doi.org/10.1002/14651858.CD011571.pub2

 Rosenbach M, Hsu S, Korman NJ, et al. Treatment of erythrodermic psoriasis: from the medical board of the National Psoriasis Foundation. J Am Acad Dermatol. 2010;62(4):655–662

https://doi.org/10.1016/j.jaad.2009.05.048

- 26. Stinco G, Errichetti E. Erythrodermic psoriasis: current and future role of biologicals. BioDrugs. 2015;29(2):91–101 <u>https://doi.org/10.1007/s40259-015-0119-4</u>
- 27. Singh RK, Lee KM, Ucmak D, Brodsky M, Atanelov Z, Farahnik B, et al. Erythrodermic psoriasis: pathophysiology and current treatment perspectives.

Psoriasis.

https://doi.org/10.2147/PTT.S101232

- Mrowietz U, Kragballe K, Reich K, Spuls P, Griffiths CE, Nast A, Franke J, Antoniou C, Arenberger P, Balieva F, et al. Definition of treatment goals for moderate to severe psoriasis: A European consensus. Arch. Dermatol. Res. 2011;303:1–10 https://doi.org/10.1007/s00403-010-1080-1
- 29. Chularojanamontri L, Silpa-archa N, Wongpraparut C, Limphoka P. Long-term Safety and Drug Survival of Acitretin in Psoriasis: A Retrospective Observational Study. Int. J. Dermatol. 2019;58:593–599 https://doi.org/10.1111/ijd.14349
- Revicki D, Willian MK, Saurat JH, Papp KA, Ortonne JP, Sexton C, Camez A. Impact of adalimumab treatment on health-related quality of life and other patient-reported outcomes: Results from a 16-week randomized controlled trial in patients with moderate to severe plaque psoriasis. Br. J. Dermatol. 2008;158:549–557 https://doi.org/10.1111/j.1365-2133.2007.08236.x
- Saurat JH, Stingl G, Dubertret L, Papp K, Langley RG, Ortonne JP, Unnebrink K, Kaul M, Camez A, Investigators CS. Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. Methotrexate vs. Placebo in patients with psoriasis (champion) Br. J. Dermatol. 2008;158:558–566 https://doi.org/10.1111/j.1365-2133.2007.08315.x
- 32. Raaby L, Zachariae C, Østensen M, Heickendorff L, Thielsen P, Grønbæk H, Skov L, Kyvsgaard N, Madsen J, Heidenheim M, et al. Methotrexate Use and Monitoring in Patients with Psoriasis: A Consensus Report Based on a Danish Expert Meeting. Acta Derm. Venereol. 2017;97:426–432 https://doi.org/10.2340/00015555-2599
- 33. Ho VC, Griffiths CE, Berth-Jones J, Papp KA, Vanaclocha F, Dauden E, Beard A, Puvanarajan L, Paul C. Intermittent short courses of cyclosporine microemulsion for the long-term management of psoriasis: A 2-year cohort study. J. Am. Acad. Dermatol. 2001;44:643–651
- Maza A, Montaudié H, Sbidian E, Gallini A, Aractingi S, Aubin F, Bachelez H, Cribier
 B, Joly P, Jullien D, et al. Oral Cyclosporin in Psoriasis: A Systematic Review on Treatment Modalities, Risk of Kidney Toxicity and Evidence for use in Non-plaque

Psoriasis. J. Eur. Acad. Dermatol. Venereol. 2011;25:19–27 https://doi.org/10.1111/j.1468-3083.2011.03992.x

- 35. Papp K, Reich K, Leonardi CL, Kircik L, Chimenti S, Langley RG, Hu C, Stevens RM, Day RM, Gordon KB, et al. Apremilast, an oral phosphodiesterase 4 (PDE4) inhibitor, in patients with moderate to severe plaque psoriasis: Results of a phase III, randomized, controlled trial (Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis [ESTEEM] 1) J. Am. Acad. Dermatol. 2015;73:37–49 https://doi.org/10.1016/j.jaad.2015.03.049
- 36. Gall JS, Kalb RE. Infliximab for the Treatment of Plaque Psoriasis. Biologics. 2008;2:115–124

https://doi.org/10.2147/BTT.S2116

- 37. Langley RG, Elewski BE, Lebwohl M, Reich K, Griffiths CE, Papp K, Puig L, Nakagawa H, Spelman L, Sigurgeirsson B, et al. Secukinumab in plaque psoriasis— Results of two phase 3 trials. N. Engl. J. Med. 2014;371:326–338 <u>https://doi.org/10.1056/NEJMoa1314258</u>
- Wang WM, Jin HZ. Biologics in the treatment of pustular psoriasis. Expert Opin Drug Saf. 2020;19(8):969–980

https://doi.org/10.1080/14740338.2020.1785427