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Psoriasis: Causes, symptoms, and novel therapeutic approaches-An updated review

Sahar Adi Albogamy

KSA, National Guard Health Affairs

Ahmad Alhelo Alanazi

KSA, National Guard Health Affairs

Hussain Mahdi Aljawad

KSA, National Guard Health Affairs

Mohammad Aljehani

KSA, National Guard Health Affairs

Meshal Saeed M Alotaibi

KSA, National Guard Health Affairs

Fouad Hamed Alamri

KSA, National Guard Health Affairs

Mohammed Saad Ali Al-Harbi

KSA, National Guard Health Affairs

Abstract--Background: Psoriasis is a chronic inflammatory skin disorder with a significant impact on patients' quality of life and is associated with various comorbidities such as psoriatic arthritis, cardiovascular diseases, and mental health issues. **Aim:** This review aims to provide an updated overview of the causes, symptoms, and novel therapeutic approaches for managing psoriasis. **Methods:** A comprehensive literature review was conducted, analyzing epidemiological, genetic, and clinical data, as well as existing treatment modalities, including traditional therapies and emerging biologics. **Results:** Psoriasis affects approximately 60 million people globally, with genetic predisposition and environmental factors contributing to its onset. The disease manifests in various forms, predominantly plaque psoriasis. Treatment strategies range from topical therapies to systemic treatments, including biologics that

target specific immune pathways, showing significant efficacy in severe cases. **Conclusion:** The management of psoriasis requires a multidisciplinary approach that includes dermatologists, rheumatologists, and mental health professionals. Novel therapies have improved outcomes, yet challenges remain in treating variants like pustular psoriasis. Continued research into genomic influences on treatment responses holds promise for personalized care.

Keywords---Psoriasis, comorbidities, treatment, biologics, immune-mediated, pustular psoriasis.

Introduction

Psoriasis is a chronic immune-mediated inflammatory dermatological condition, linked to various comorbidities including psoriatic arthritis, mental health disorders, cardiovascular conditions, and liver diseases. In 2014, the World Health Organization classified psoriasis as a significant non-communicable disease, emphasizing the issues arising from misdiagnosis, inadequate management, and the social stigma associated with the condition. [1] According to the Global Burden of Disease Study, psoriasis contributed to approximately 5.6 million disability-adjusted life-years (DALYs) across all ages in 2016, which is at least three times greater than the burden posed by inflammatory bowel disease. [2]

Epidemiology:

Both genders are affected by psoriasis, though females tend to experience earlier onset, particularly in individuals with a familial history of the disease. The age of onset follows a bimodal distribution, with peaks occurring between 30-39 years and 60-69 years for males, while women typically present symptoms a decade earlier. [3] Approximately 60 million individuals worldwide are estimated to suffer from psoriasis, with prevalence rates differing by country, ranging from 0.05% of the general population in Taiwan to 1.88% in Australia. [3][4] The condition is more prevalent in high-income regions and among older demographics. [3] In the United Kingdom, the incidence rate stands at 1.52% within the general population.

Aetiology:

The development of psoriasis is influenced by multiple factors, with genetic predisposition being a significant contributor, especially in patients with early-onset plaque psoriasis (onset before 40 years). This is supported by studies involving twins, family lineages, and extensive population data, which estimate heritability to be between 60-90%. [5] More than 60 susceptibility loci have been identified through genome-wide association studies. [5] Many of these candidate genes are associated with processes such as antigen presentation (HLA-C and ERAP1), NF-kappa B signaling (TNIP1), the type 1 interferon pathway (RNF113 and IFIH1), the interleukin (IL)-23/Th17 axis (IL23R, IL12B, and TYK2), and skin barrier integrity (LCE3). [5] This indicates a complex interaction among T cells,

dendritic cells, and keratinocytes as key elements driving the pathophysiology of psoriasis, with the IL-23/Th17 axis playing a pivotal role in immune activation, persistent inflammation, and keratinocyte hyperproliferation. [6] Various environmental factors, such as obesity, stress, beta-blocker use, smoking, and lithium, have been recognized to worsen psoriasis symptoms. [7] Although data is somewhat limited, pustular psoriasis appears to have a distinct genetic profile, with different susceptibility genes involved (such as IL36RN and AP1S3 in individuals of European ancestry, along with CARD14). [5][6][7][8].

Clinical Presentations:

Psoriasis presents in various forms, including plaque, flexural, guttate, pustular, and erythrodermic psoriasis. The most prevalent type is plaque psoriasis, characterized by well-defined, salmon pink plaques covered with silvery-white scales. These plaques typically appear symmetrically on extensor surfaces, such as the elbows and knees, as well as on the trunk and scalp. The Auspitz sign may be observed, indicating bleeding points where the scales have been removed. Flexural psoriasis typically lacks significant scaling and can affect areas such as the axillae, submammary regions, and genital areas. Guttate psoriasis presents as an acute, symmetrical eruption of drop-like papules and plaques primarily affecting the trunk and limbs, and is classically, though not exclusively, preceded by a streptococcal infection. Individuals with guttate psoriasis may later develop plaque psoriasis. In rare instances of severe, uncontrolled psoriasis, patients may experience a widespread erythematous rash known as erythroderma, which poses life-threatening risks such as hypothermia, infection, acute kidney injury, and high-output cardiac failure. The Koebner phenomenon describes the onset of psoriasis in areas of the skin that have experienced trauma. Additionally, up to 50% of patients may experience nail involvement, which can manifest as nail pitting (indentations), onycholysis (separation of the nail plate from the nail bed), oil spots (discoloration of the nail bed), dystrophy, and subungual hyperkeratosis.

Multimorbidity and Psoriasis:

Multimorbidity, defined as the coexistence of two or more chronic conditions, is prevalent among individuals with psoriasis. Psoriatic arthritis (PsA) impacts up to 30% of patients with psoriasis, particularly those exhibiting nail dystrophy or scalp, intergluteal, or perianal psoriasis. [9] PsA is a heterogeneous condition that can present as seronegative asymmetric oligoarthritis, enthesitis, or dactylitis. Typically, psoriasis precedes the onset of joint disease by as much as 10 years, enabling general practitioners and dermatologists managing psoriasis to facilitate early diagnosis of PsA. The Psoriasis Epidemiology Screening Tool (PEST), a validated five-item questionnaire, is recommended for screening for PsA. [10] Individuals with psoriasis are at a higher risk of developing comorbidities such as obesity, cardiovascular disease, non-alcoholic fatty liver disease, diabetes, and metabolic syndrome compared to the general population, with risks particularly heightened among those with more severe forms of psoriasis. [11] This elevated risk may stem from shared genetic predispositions, inflammatory pathways, and common risk factors. [12][13] Consequently, patients with severe psoriasis exhibit increased mortality rates, primarily due to cardiovascular complications. [14] However, this situation is potentially modifiable, as aggressive treatment of

psoriasis has been shown to enhance cardiovascular outcomes. [15] Furthermore, the incidence of mental health disorders, including anxiety and depression, is significantly higher in patients with psoriasis relative to the general population, underscoring the psychosocial burdens associated with the condition. [16]

Assessment of Patients with Psoriasis

The assessment of psoriasis involves evaluating the extent of skin involvement (measured by body surface area, BSA) and the severity of erythema, induration, and scaling. In secondary care settings, validated tools like the Psoriasis Area Severity Index (PASI) and the Physician Global Assessment Scale are routinely employed, alongside patient-reported outcome measures such as the Dermatology Life Quality Index (DLQI). [17][18] Recognizing the psychological impact of psoriasis is crucial, as it may lead to treatment disengagement and non-adherence. Each patient encounter serves as an opportunity to screen for multimorbidities, which, in addition to improving overall health, may influence treatment decisions for psoriasis. For example, the presence of chronic liver disease may contraindicate the use of methotrexate. [19] Thus, a multidisciplinary approach involving rheumatologists, hepatologists, and clinical psychologists is essential for comprehensive patient care.

Treatment for Psoriasis

Therapeutic options for psoriasis include topical therapy, phototherapy, and systemic treatments, as outlined in the UK National Institute for Health and Care Excellence (NICE) guidelines. Treatment goals aim for a 75% (PASI75) or 90% (PASI90) improvement in PASI scores, correlating to absolute PASI scores of ≤ 4 or ≤ 2 , respectively. [20]

Topical Therapies:

First-line treatments typically involve topical therapies such as vitamin D analogues (e.g., calcipotriol) and corticosteroids. The efficacy of topical treatments can be enhanced through occlusion or combination therapy (e.g., calcipotriol/betamethasone). While previously popular, dithranol and tar preparations are now less commonly used due to their potential to stain and irritate the skin. Psoriasis located on difficult-to-treat areas (e.g., scalp, face, nails, genitalia, palms, and soles) requires special attention due to its significant functional impact and relatively poor treatment response. When treating the face or genitalia, low-potency steroids should be used for a limited duration to minimize the risk of skin atrophy and telangiectasia.

Second-Line Therapies::

Second-line options include phototherapy (narrowband ultraviolet B radiation, NB-UVB, and psoralen with ultraviolet A radiation, PUVA) and conventional systemic agents such as methotrexate, ciclosporin, and acitretin. NB-UVB has largely replaced PUVA due to concerns regarding the skin cancer risk associated with cumulative PUVA doses. [21] Methotrexate functions by inhibiting lymphocyte proliferation through multiple mechanisms, including dihydrofolate

reductase inhibition, blockade of aminoimidazole carboxamide ribotide transformylase (AICARTase), and adenosine accumulation. The most serious adverse effect of methotrexate is bone marrow suppression, while other potential complications include nausea, pneumonitis, hepatitis, liver fibrosis, and teratogenicity. Methotrexate is usually administered orally on a weekly basis, though a subcutaneous formulation can reduce gastrointestinal side effects and enhance efficacy due to higher bioavailability. [22] Cyclosporin, a calcineurin inhibitor, has a rapid onset of action but may lead to hypertension and irreversible renal toxicity. Acitretin, an oral retinoid, promotes keratinocyte differentiation and can cause side effects like dry skin, hair loss, hyperlipidaemia, and hepatotoxicity. Both methotrexate and acitretin are contraindicated during pregnancy. [23]

For cases refractory to methotrexate and/or cyclosporin or where second-line therapies are unsuitable, biologic therapies or oral small molecule inhibitors may be considered. Biologics, which are monoclonal antibodies or soluble receptors targeting pro-inflammatory cytokines, have significantly improved outcomes in moderate to severe psoriasis. Several biologic therapies are approved for use in this patient population, including TNF inhibitors (adalimumab, etanercept, infliximab, and certolizumab), IL-12/23p40 inhibitors (ustekinumab), IL-23p19 inhibitors (risankizumab, guselkumab, and tildrakizumab), IL-17 inhibitors (ixekizumab and secukinumab), and IL-17 receptor inhibitors (brodalumab). There is no single 'best' biologic; the choice must be tailored to each patient's specific needs. [24][25]

Current treatment decisions primarily depend on clinical factors such as disease phenotype, the presence of psoriatic arthritis, prior biologic treatment outcomes, comorbidities (e.g., demyelinating disease and inflammatory bowel disease), drug-specific considerations (e.g., dosing frequency), and lifestyle factors (e.g., conception plans). [24] Genomic information may guide effective therapy deployment in the future, representing an active area of research. [26] While biologics are highly effective, they necessitate regular subcutaneous or intravenous administration. Oral small molecule inhibitors like apremilast (a phosphodiesterase 4 inhibitor) and dimethyl fumarate are approved for moderate to severe psoriasis, with ongoing trials exploring small molecules that block tyrosine kinase 2 in the Janus kinase (JAK) - signal transducer and activator of transcription (STAT) pathway.

Pustular Psoriasis

Pustular psoriasis is a distinct phenotype characterized by the presence of sterile pustules. It can manifest in several forms:

- **Generalized Pustular Psoriasis (GPP):** This acute variant presents with a widespread eruption of superficial pustules on erythematous skin and may be accompanied by systemic symptoms such as fever. Laboratory tests often reveal neutrophilia and elevated inflammatory markers, indicating a significant inflammatory response. GPP can be life-threatening due to the risk of complications associated with the acute pustular eruption.

- **Acrodermatitis Continua of Hallopeau (ACH):** This form is localized primarily to the digits and is characterized by recurrent pustular lesions at the tips of the fingers and toes.
- **Palmoplantar Pustulosis (PPP):** This type affects the palms of the hands and soles of the feet, leading to the formation of pustules and significant discomfort, which can severely impact daily activities.

Treatment for Pustular Psoriasis:

Despite the increasing availability of treatments for plaque psoriasis, effective management options for pustular psoriasis remain limited, and this condition represents an area of high unmet therapeutic need. Both PPP and ACH are known to be particularly resistant to the standard therapies used for plaque psoriasis.

1. **First-Line Treatments:**
 - **Topical Steroids:** Potent topical corticosteroids combined with occlusion are typically the first-line treatment for localized forms of pustular psoriasis.
2. **Phototherapy:**
 - **PUVA** (psoralen with ultraviolet A) may be considered for managing palmoplantar pustulosis, although it is generally less effective compared to its use in plaque psoriasis.
3. **Systemic Treatments:**
 - For more severe or resistant cases, systemic treatments are often necessary. For acute severe GPP, rapid intervention may be required, utilizing medications such as ciclosporin or infliximab due to their quick onset of action.

Advances in Treatment:

Recent research has enhanced our understanding of the pathogenic mechanisms underlying GPP, particularly regarding the role of IL36RN mutations. These insights have led to the development of IL-36 receptor inhibitors, which are currently undergoing clinical trials. [28][29] These new therapies represent a promising direction for addressing the treatment gaps in pustular psoriasis and may offer more targeted and effective management strategies in the future.

Psoriasis and IL-36:

IL-36 is a group of pro-inflammatory cytokines that belong to the interleukin-1 (IL-1) family. The IL-36 family consists of three members: IL-36 α , IL-36 β , and IL-36 γ . These cytokines are primarily produced by immune cells and are involved in the regulation of immune responses, particularly in inflammatory conditions. Here's a breakdown of key aspects of IL-36:

Functions of IL-36

1. **Pro-inflammatory Role:** IL-36 cytokines promote the activation of immune cells and enhance the production of other pro-inflammatory cytokines. This contributes to the inflammatory response seen in various diseases.

2. **Receptor Interaction:** IL-36 exerts its effects by binding to the IL-36 receptor (IL-36R), which is expressed on various immune and non-immune cells. This interaction triggers downstream signaling pathways that amplify the inflammatory response.
3. **T Cell Activation:** IL-36 cytokines can activate T cells, especially T helper 17 (Th17) cells, which play a significant role in the pathogenesis of autoimmune and inflammatory diseases, including psoriasis.

Role in Disease:

IL-36 has been implicated in several inflammatory skin conditions, particularly psoriasis and generalized pustular psoriasis (GPP). Research has shown that:

- **Psoriasis:** Elevated levels of IL-36 have been found in the skin lesions of patients with psoriasis, suggesting that it contributes to the inflammatory environment in this condition.
- **Generalized Pustular Psoriasis (GPP):** Mutations in the IL36RN gene, which encodes the IL-36 receptor antagonist, have been linked to GPP. These mutations can lead to uncontrolled activation of IL-36 signaling, resulting in the acute inflammatory response characteristic of GPP.

Therapeutic Implications:

Given the role of IL-36 in driving inflammation, targeting the IL-36 pathway has emerged as a potential therapeutic strategy for treating inflammatory diseases, particularly psoriasis.

- **IL-36 Receptor Inhibitors:** New treatments that specifically inhibit IL-36 receptor signaling are being developed and tested in clinical trials, aiming to provide more effective therapies for patients suffering from IL-36-mediated inflammatory conditions.

Overall, IL-36 plays a critical role in mediating inflammatory responses, and its dysregulation is associated with various autoimmune and inflammatory disorders.

IL36RN mutations:

IL36RN mutations are primarily caused by genetic alterations in the IL36RN gene, which encodes the interleukin-36 receptor antagonist (IL-36Ra). These mutations can lead to a loss of function or dysfunctional forms of the IL-36Ra protein, resulting in uncontrolled activation of the IL-36 signaling pathway. Here are some key aspects regarding the causes and implications of IL36RN mutations:

Causes of IL36RN Mutations

1. **Genetic Inheritance:**
 - **Autosomal Dominant Inheritance:** Some IL36RN mutations are inherited in an autosomal dominant manner, meaning that a single copy of the mutated gene from one parent can lead to the manifestation of the disease. This can occur even if the other copy of the gene is normal.

- **De Novo Mutations:** In some cases, mutations can occur spontaneously (de novo) in an individual without a family history of the disorder. This means that the mutation arises in the germline cells (sperm or egg) of one of the parents or early in embryonic development.
- 2. **Environmental Factors:**
 - While IL36RN mutations are primarily genetic, environmental factors may play a role in triggering symptoms or exacerbating conditions associated with these mutations. For instance, infections, stress, and skin trauma can potentially influence the inflammatory response in individuals with IL36RN mutations, especially in conditions like generalized pustular psoriasis (GPP).
- 3. **Population Variability:**
 - Certain populations may have a higher prevalence of specific IL36RN mutations due to genetic drift, founder effects, or other demographic factors. For instance, some studies indicate that mutations in IL36RN are more common in certain ethnic groups.

Implications of IL36RN Mutations

1. **Pathogenesis of Generalized Pustular Psoriasis (GPP):**
 - IL36RN mutations are strongly associated with GPP, leading to an uncontrolled inflammatory response due to the lack of effective inhibition of IL-36 signaling. This results in acute episodes of widespread pustular lesions, systemic symptoms, and can be life-threatening.
2. **Other Skin Conditions:**
 - While primarily linked to GPP, IL36RN mutations may also contribute to other inflammatory skin conditions, although their exact role in these disorders may require further research.
3. **Potential for Targeted Therapies:**
 - Understanding IL36RN mutations opens avenues for targeted treatments. Therapeutics aimed at inhibiting IL-36 signaling are being developed and tested, offering hope for more effective management of conditions associated with these mutations.

In summary, IL36RN mutations arise mainly from genetic alterations that can be inherited or occur spontaneously. These mutations significantly impact the regulation of inflammatory responses, particularly in conditions like generalized pustular psoriasis.

Advanced Treatment Lines:

Recent advances in psoriasis treatment have led to the development of new therapies that offer more effective management for patients with moderate to severe forms of the disease. Here's an overview of some of the latest treatments:

1. Biologic Therapies

Biologics are a class of medications derived from living organisms and target specific components of the immune system. The following are some newly approved biologic treatments for psoriasis:

- **IL-23 Inhibitors:** These target interleukin-23, a cytokine involved in inflammatory responses. Notable examples include:
 - **Guselkumab (Tremfya):** Approved for moderate to severe plaque psoriasis, it has shown sustained efficacy and safety.
 - **Rizankizumab (Skyrizi):** Another IL-23 inhibitor that has demonstrated effectiveness in clinical trials for psoriasis.
 - **Tildrakizumab (Ilumya):** Targets IL-23 and is used for moderate to severe plaque psoriasis.
- **IL-17 Inhibitors:** These inhibit interleukin-17, which plays a significant role in the inflammatory process of psoriasis. Key agents include:
 - **Secukinumab (Cosentyx):** Approved for various inflammatory conditions, including psoriasis, and is effective for skin and joint symptoms.
 - **Ixekizumab (Taltz):** Targets IL-17A and has been shown to provide rapid and sustained improvement in psoriasis.
- **IL-36 Receptor Antagonists:** New research has focused on the role of IL-36 in psoriasis, leading to the development of targeted therapies:
 - **Breztri (Anakinra):** Anakinra is an IL-1 receptor antagonist that has shown promise in treating skin manifestations of systemic diseases, including psoriasis, though it is primarily used for rheumatoid arthritis.

2. Oral Small Molecule Inhibitors

These medications can be taken orally and work by inhibiting specific pathways involved in the inflammatory response.

- **Apremilast (Otezla):** A phosphodiesterase-4 (PDE4) inhibitor, this oral medication reduces inflammation and has been used for psoriasis and psoriatic arthritis. New studies are investigating its use in combination with biologics.
- **Tofacitinib (Xeljanz):** A Janus kinase (JAK) inhibitor that is primarily used for rheumatoid arthritis and ulcerative colitis. Research is ongoing regarding its effectiveness in treating psoriasis.

3. Topical Treatments

There have also been advancements in topical therapies:

- **New Combination Topicals:** Advances in formulations combining traditional agents, such as corticosteroids with vitamin D analogs, provide enhanced efficacy and improved patient adherence.
- **Nanotechnology:** Research is exploring the use of nanoparticles in topical formulations to enhance drug delivery and efficacy while reducing side effects.

4. Gene Therapy and Innovative Approaches

Though still largely experimental, gene therapy and other innovative approaches are being explored to target the underlying genetic mechanisms of psoriasis.

- **CRISPR Technology:** Research is being conducted on the use of CRISPR to modify genes associated with psoriasis, potentially leading to more permanent solutions.

5. New Treatment Guidelines

Recent updates to treatment guidelines by organizations like the National Psoriasis Foundation and the American Academy of Dermatology emphasize personalized treatment plans, integrating patient preferences, and considering comorbidities. The landscape of psoriasis treatment continues to evolve, with new

biologics, oral therapies, and topical treatments providing hope for improved outcomes. Patients should consult with their healthcare providers to explore the best treatment options tailored to their specific needs and conditions.

Conclusion

Psoriasis is a multifaceted condition influenced by genetic, environmental, and immunological factors. The understanding of psoriasis has evolved significantly, leading to improved management strategies. The condition's prevalence worldwide underscores its importance as a public health concern, affecting approximately 60 million individuals. The bimodal age distribution of onset highlights the need for early recognition and intervention, particularly among younger populations. Genetic studies have identified multiple susceptibility loci, revealing the complexity of the disease's pathophysiology. Notably, the IL-23/Th17 pathway has emerged as a pivotal target for new therapies, driving advancements in biologic treatments that have transformed the management of moderate to severe psoriasis. Biologics, including IL-17 and IL-23 inhibitors, offer targeted interventions that lead to significant improvements in patients' quality of life, addressing the underlying immunological drivers of the disease. Despite these advancements, challenges persist, particularly with variants such as pustular psoriasis, which remain difficult to treat. The lack of effective therapies for pustular forms emphasizes the unmet need in this area. Current therapeutic approaches must consider comorbidities, which are prevalent among psoriasis patients, complicating management. The integration of dermatologists, rheumatologists, and mental health professionals is essential for delivering comprehensive care and improving treatment adherence. Future research into the genetic basis of psoriasis and the development of personalized medicine will be crucial in optimizing treatment strategies. The evolution of treatment options, alongside a growing understanding of psoriasis as a systemic disease, highlights the need for a holistic approach that not only addresses skin symptoms but also considers the broader health implications of the condition. Continued efforts to raise awareness and reduce stigma associated with psoriasis will further enhance the quality of care for affected individuals.

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الصدفية: الأسباب، الأعراض، والنهج العلاجي الجديد - مراجعة محدثة

الملخص:

الخلفية: الصدفية هي اضطراب جلدي التهابي مزمن يؤثر بشكل كبير على جودة حياة المرضى وترتبط بمختلف الأمراض المصاحبة مثل التهاب المفاصل الصدفي، وأمراض القلب والأوعية الدموية، ومشاكل الصحة النفسية.

الهدف: يهدف هذه المراجعة إلى تقديم نظرة شاملة محدثة حول أسباب وأعراض النهج العلاجي الجديد لإدارة الصدفية.

الطرق: تم إجراء مراجعة شاملة للأدبيات، مع تحليل البيانات الوبائية، الوراثية، والسريرية، بالإضافة إلى العلاجات الحالية، بما في ذلك العلاجات التقليدية والبيولوجيات الناشئة.

النتائج: تؤثر الصدفية على حوالي 60 مليون شخص على مستوى العالم، مع وجود استعداد وراثي وعوامل بيئية تسهم في ظهورها. تتجلى هذه الحالة في أشكال مختلفة، وتعد الصدفية اللويحية هي الأكثر شيوعًا. تتراوح استراتيجيات العلاج من العلاجات الموضعية إلى العلاجات الجهازية، بما في ذلك البيولوجيات التي تستهدف مسارات مناعية محددة، والتي أظهرت فعالية كبيرة في الحالات الشديدة.

الخلاصة: تتطلب إدارة الصدفية نهجًا متعدد التخصصات يشمل أطباء الجلد، وأطباء الروماتيزم، والمهنيين في الصحة النفسية. لقد حسنت العلاجات الجديدة النتائج، ولكن لا تزال هناك تحديات في علاج الأنواع مثل الصدفية البثرية. يحمل البحث المستمر في التأثيرات الجينومية على استجابات العلاج أملاً للرعاية الشخصية.

الكلمات المفتاحية: الصدفية، الأمراض المصاحبة، العلاج، البيولوجيات، المناعة، الصدفية البثرية.